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SOME SURGICAL ASPECTS OF HISTOPLASMOSIS*

Two Cases of Splenectomy

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SINCE Darling's[1] description of histoplasmosis in 1906, the medical aspects of the disease have been studied extensively. Only recently have surgeons realized that certain types of the disease, or its complications, may require surgical therapy.

In 1948 Bunnell and Furcolow[2] recorded a case of lobectomy for repeated bleeding from the right lower lobe of the lung. A bronchopleural fistula developed. Eight weeks after the lobectomy, attempt was made to repair the fistula which resulted in death from shock. This patient had a proved diagnosis of histoplasmosis and tuberculosis.

Two years later (July, 1950), in an excellent review of histoplasmosis, Hodgson, Weed and Clagett[3] described a case of lung cavitation which was treated by lobectomy with recovery. A diagnosis of histoplasmosis was made after the operation. Tuberculosis was not found in the removed lobe of the lung. On histologic examination, *Histoplasma capsulatum* was found in the cytoplasm of fibroblasts and in phagocytes. A second lobectomy for lung cavitation was recorded later by these authors[4] in 1951. No evidence of tuberculosis was found. The first patient was alive and working two years after operation and the second was reported by Bettag[5] as having no evidence of recurrence of disease 16 months after operation. In a discussion of the second report by Hodgson, Weed and Clagett,[6] Duryea described a case of histoplasmosis treated by lobectomy for

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cavitation in which tuberculosis was not found. Furcolow[7] reported 3 other cases with lung cavitation without evidence of tuberculosis which were not operated upon.

In October 1950 Raftery, Trafas and McClure[8] discussed histoplasmosis in its relation to appendicitis. These authors postulated that histoplasmosis is an important factor in appendicitis and mesenteric adenitis and concluded that histoplasmosis causes a lymphoid hyperplasia and by this mechanism is a cause of chronic and acute appendicitis. A review of 2,135 cases of appendicitis and mesenteric adenitis was made and revealed a 5 per cent incidence of histoplasmosis in appendicitis and a 43 per cent incidence in mesenteric adenitis. Raftery[7] made a later study of appendices removed from children under 16 years of age. Of 436 appendices examined, 54 (12 per cent) were found to contain *Histoplasma capsulatum*. Of the 54 involved cases, 36 ran a low grade fever and 30 gave a history of recurrent abdominal pain and nausea.

Several cases of histoplasmosis of the larynx have been reported.[7,10,11,12,13] Such cases are important because they must be differentiated from carcinoma. Laryngeal lesions are usually associated with other evidence of the disease in the mucous membranes of the tongue, mouth and pharynx and in the lungs. Dean[14] and Furcolow reported cases of laryngeal obstruction requiring tracheotomy. Both cases suggested a diagnosis of carcinoma. In a case recorded by Parsons and Zarafonetis, dysphagia developed as a result of extension of the disease in the pharynx and a gastrostomy was made to feed the patient.

Ulcers on the tongue have been described by several authors.[10,13,15,16,17,18] These ulcers have, in some cases, simulated carcinoma and the diagnosis has been proved by biopsy specimen. Others[10,12,13,16,17,19] have described ulcers on the lip, in the nares, in the auditory canal and on the penis. Carcinoma has been excluded by biopsy specimen in these cases. Associated with such ulcerations, Curtis and Grekin have described nodules in the skin. Furcolow mentions a case in which *Histoplasma capsulatum* was found in removed tonsils 18 months after operation.

Joints may be infected and simulate tuberculosis. Key and Large[20] described a patient who had an amputation above the knee for a serious knee infection. A study of the joint tissue proved the infection to be histoplasmosis.

Ulceration of the colon simulating ulcerative colitis has been recorded. Henderson, Pinkerton and Moore[21] studied such a case which proved at autopsy to have extensive ulceration of the colon and terminal ileum. An obscure malignancy had been suspected.

The cause of death was due to perforation of the colon which produced general peritonitis.

An enlarged spleen in a 7 months old female led to the diagnosis of splenic anemia (Amolsch and Wax).[22] A splenectomy was done without benefit and the patient died three weeks later. A diagnosis of histoplasmosis was not made until the spleen was examined for the organism several months later.

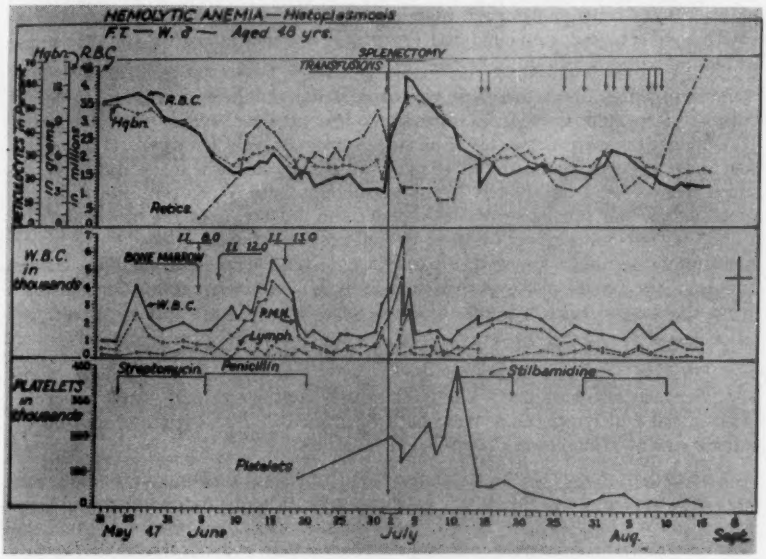

Chart 1. Graphic illustration of the hematologic data in case 1 of splenomegaly due to histoplasmosis. In addition to the hemolytic anemia, there was a leukopenia and a thrombocytopenia with only a temporary response following splenectomy.

Report of Two Cases of Splenectomy

Bunnell and Furcolow summarized previously the following 2 cases in *Public Health Reports* for March 5, 1948. A more complete review of these cases follows:

Case 1. F. T., a white male, aged 48 years, was admitted to the University of Kansas Medical Center on May 20, 1947, with the complaints of weakness, anorexia, chills and fever. The onset of weakness was about two and one-half years prior to this admission, at which time he was found to be anemic and a roentgenogram of the chest revealed a pulmonary infiltration. A short time thereafter he developed jaundice and his urine was very dark. Transfusions were given with some improvement. The jaundice persisted for about one year. About four weeks prior to the present admission he noted loss of appetite, moderately productive cough, chills and fever. The urine was extremely dark for a week prior to admission.

Physical examination on admission revealed a thin, somewhat emaciated individual. The only positive findings were moist rales in the left midlung field and increased breath sounds in the left apex. The spleen was palpable on inspiration only, extending just inferior to the costal margin.

The hematologic data are summarized in chart 1. A complete blood examination on June 4, 1947, showed a marked anemia of the normochromic normocytic type, a slight increase in reticulocytes (4.0 per cent), a severe leukopenia, 1,550 leukocytes per cu. mm., differential count; polymorphonuclear leukocytes 32 per cent, lymphocytes 50 per cent, monocytes 16 per cent, eosinophiles 2.0 per cent, and normal platelets, 280,000 per cu. mm. A sternal marrow biopsy revealed a myeloid and erythroid hyperplasia with a slight increase in monocytes and reticulum cells.

A roentgenogram of the chest was interpreted as bilateral pulmonary tuberculosis. Repeated sputum examinations for tubercle bacilli were negative. Blood cultures were negative. The spleen progressively enlarged. The reticulocyte count became elevated to 48 per cent, the anemia was marked, the icterus index was 14 u., fragility test beginning hemolysis 0.37 per cent and not complete at 0.27 per cent, a severe leukopenia and a decrease in the blood platelets to 86,000 per cu. mm. was noted. A diagnosis was made of secondary hyperplenism, cause unknown, with a pancytopenia with hemolytic anemia. Unfortunately, the report of a positive culture of *Histoplasma capsulatum* obtained from the gastric juice was not received until a few hours following surgery.

The patient was operated upon July 2, 1947, and a very large spleen, weighing 990 Gm., and one accessory spleen were removed. A lymph node biopsy specimen was also obtained. The liver grossly contained small visible tubercles. The spleen and lymph node were both diagnosed by histologic and culture examinations as *Histoplasma capsulatum* infection.

The patient survived the operation. Multiple transfusions were given during and immediately following splenectomy. The hematologic picture improved only temporarily (chart 1) and the reticulocytosis, severe anemia, leukopenia, and thrombocytopenia grew progressively worse. He died Sept. 8, 1947, two months after splenectomy.

An autopsy was performed which revealed granulomatous lesions of the lungs, liver, adrenal glands, gastrointestinal tract, abdominal and thoracic lymph nodes, heart, and bone marrow. Cultures of the lung and adrenal glands were positive for acid-fast organisms and innoculated guinea pigs were positive for tuberculosis. Of 13 different organs cultured for pathogenic fungi, 12 were positive for *Histoplasma capsulatum*. Histologic examination revealed the typical yeastlike organisms in the liver, kidneys, adrenal gland, bone marrow, small intestine, and lymph nodes.

Case 2. S. P., a white female aged 20 months, was admitted to the University of Kansas Medical Center on May 21, 1947, with the complaint of an enlarged abdomen. The enlargement was first noticed in January, 1947, at which time the child had influenza. No previous illness had occurred. By May 1947 the abdomen was very large and the family doctor was consulted. Transfusions were given and the patient was referred to the University of Kansas Medical Center.

Physical examination on admission revealed an emaciated white female child who appeared to be chronically ill. A generalized lymphadenopathy was noted, the lymph glands being small. The abdomen was very much distended and a

large mass filled the entire left side of the abdomen, extending to the symphysis pubis and to the right of the umbilicus to the right anteriorsuperior iliac spine. The liver was enlarged and extended about 5 cm. below the costal margin. A tourniquet test was positive in 30 seconds.

Initial laboratory tests were as follows: Erythrocyte count 3,540,000 per cu. mm., hemoglobin 7.7 Gm., reticulocytes 5.6 per cent, leukocyte count 5,500 per cu. mm., with the following differential count: polymorphonuclear leukocytes 37 per cent (33 per cent filamented, 4 per cent band forms), 3 metamyelocytes and 1 myelocyte, lymphocytes 47 per cent, eosinophiles 1 per cent, monocytes 9 per cent, and basophiles 2 per cent. The platelets were 127,000 per cu. mm. Occasional nucleated red cells were observed. Red cell fragility test showed beginning hemolysis at 0.43 per cent and complete hemolysis at 0.28 per cent. The Wassermann and Kahn tests were negative. A bone marrow biopsy specimen showed normal marrow tissue.

Roentgenograms of the chest revealed a normal heart and lung field. The long bones were normal. The abdomen showed an enlarged mass which was thought to be a kidney because of an inconclusive barium enema and an intravenous pyelogram showing a defect.

The hospital course was of interest. During the first 20 days the patient did very well. The temperature at times was 100 F. per rectum. A diagnosis of Wilm's tumor was made and a series of roentgenologic treatments were given to the abdominal mass with a total of 2,587 roentgens received in about four weeks. The platelets gradually decreased to 22,000 per cu. mm. and the leukocyte count to 2,150 per cu. mm. Numerous small transfusions were given. On the sixty-fourth hospital day the patient began to have a daily septic temperature of 104.2 F. maximum and 98.6 F. minimum. The appetite was poor and parenteral fluids were given. Retrograde pyelograms were then done and interpreted as normal. An adrenalin test showed an increase in the leukocyte count and a decrease in the size of the mass. A diagnosis was then made of splenomegaly of unknown etiology, with secondary hypersplenism. A splenectomy was done on Aug. 18, 1947. The weight of the spleen was 510 Gm. The liver grossly appeared fibrotic. Liver and lymph node specimens for biopsies were obtained. The patient improved but the platelet count remained about 38,000 per cu. mm. The liver grew progressively larger and extended to the iliac crest.

The histopathologic interpretation of the surgical specimens was granulomatous lesions of the abdominal lymph nodes, spleen and liver. *Histoplasma capsulatum* was cultured from the spleen.

On Sept. 10, 1947, the blood count was as follows: Erythrocyte count 5,890,000 per cu. mm., hemoglobin 16.0 Gm., differential count; polymorphonuclear leukocytes 65 per cent (54 per cent filamented and 11 per cent band forms), lymphocytes 32 per cent, and metamyelocytes 3 per cent. The reticulocytes were 2.6 per cent and the platelets only 52,000 per cu. mm.

The patient was dismissed from the hospital after 114 days of observation and treatment. She was observed on Feb. 18, 1950, and clinically was doing well. The complement fixation test for histoplasmosis at that time was negative on one test and 1 plus on another. Prior tests had been 4 plus. A roentgenogram of the chest revealed a granular type of calcification about 1.0 cm. in diameter in the right middle lobe. A few small deposits were observed in the adjacent lung. Otherwise the lung fields were normal. A communication

received Oct. 23, 1951, stated that the child was in the first grade at school and living a normal life.

Discussion

Evidence is recorded that almost every organ in the body has been infected with *Histoplasma capsulatum*. It is not infrequently associated with other diseases. This observation has led Weidman[23] to state: "I think the time is ripe to advance the theory, at least, that pre-existing, particularly granulomatous diseases, can act as predisposing factors for the superimposition of a fungus infection."

The association of histoplasmosis with other diseases prompted Furcolow to say: "Certainly, one of the most pressing questions is how to evaluate the diagnostic significance of the recovery of the fungus in the presence of other disease. Should it be considered an accidental finding of academic rather than practical importance, or does the presence of the fungus influence in some way the onset or course of the predominant clinical disease?"

So many cases of histoplasmosis have been recorded to date without evidence of other disease that it seems certain that infection with this fungus is a definite clinical entity. That there is some doubt about the disease in some reports is shown by a remark by Hirsch[24] in a discussion of Raftery's report on the presence of *Histoplasma capsulatum* in appendicitis. Hirsch states: "It seems to me that more evidence of the character of the inclusions and that they are actually *Histoplasma capsulatum* is needed."

The importance of differentiating histoplasmosis from other diseases cannot be questioned. While this infection may be classed as "subclinical" in some cases, the infection with symptoms is of great importance because of the high death rate. Beadenkopf and Loosli[25] have stated: "The whole gamut of illness severity, from a symptomless infection to a rapidly fatal generalized infection, seems to characterize histoplasmosis." It is well known that the spleen, lymph nodes, bone marrow and liver are frequently involved. Of 71 cases reviewed by Parsons and Zarafonetis, 37 had enlarged spleens.

After a study of the 2 cases of splenectomy reviewed above we have asked ourselves the following questions:

1. Does histoplasmosis tend to produce hypersplenism and lower the blood platelet count? If so, does the platelet count return to normal after splenectomy?

2. Is there ever a bleeding tendency in histoplasmosis?

3. Does histoplasmosis produce secondary thrombocytopenic purpura in acute cases?

4. Is splenectomy ever indicated in histoplasmosis?

Certainly the above 2 cases, from a clinical and laboratory evaluation, were consistent with our present-day concept of secondary hypersplenism in that the bone marrow was normal or hyperplastic, one or more of the peripheral formed elements of the blood were markedly decreased, and an enlarged spleen was present. The hematologic improvement following splenectomy was minimal in both patients.

There has been no evidence of a bleeding tendency in histoplasmosis with enlarged spleen.

Thrombocytopenic purpura has not been found in acute cases of histoplasmosis with splenomegaly.

In the present state of our knowledge we cannot say with assurance that splenectomy influences the progress of histoplasmosis although 1 of our 2 cases recovered.

Conclusions

The principal surgical aspects of histoplasmosis have been discussed. The evidence is clear that operation may be necessary or advisable in certain types of the disease.

The number of cases in which splenectomy was a part of the treatment of histoplasmosis is too small to definitely evaluate such therapy.

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MANAGEMENT OF THYROID CARCINOMA

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Because of recent developments, a reconsideration of carcinoma of the thyroid gland appears to be warranted. Carcinoma of the thyroid presents a wide variety of clinical and histologic forms, each of which is associated with a fairly constant pattern of clinical behavior. This latter observation represents the basis for selection of an appropriate plan of management.

The number of patients with carcinoma of the thyroid appears to be increasing. The increased incidence is largely the result of an appreciation of the nature of "lateral aberrant thyroid disease." Formerly, thyroid tissue in the neck, unassociated with the thyroid gland, was often interpreted as an embryologic rest; a remnant of thyroid tissue growing where it lodged in its descent from the branchial pouches to its usual position. Thyroid tissue in the neck away from the gland itself represents replacement of a lymph node by a metastasizing carcinoma of the thyroid. This may occur without enlargement of the thyroid gland.

Much has been written about the histology of carcinoma of the thyroid, but a generally accepted classification has not yet been evolved. This discrepancy represents more a difference in the choice of a nomenclature rather than a lack of appreciation of the main histologic types. A practical classification of carcinoma of the thyroid is given in table 1.

About 50 per cent of all carcinomas of the thyroid are papillary in type (fig. 1). Papillary tumors often have a prolonged clinical course. However, there are notable exceptions in the clinical behavior of this group. Frazell and Foote[17] reported that, of 130 patients followed five years or more with papillary adenocarcinoma of the thyroid, 21 per cent died of their disease. Of the group that died, the average lapse of time from diagnosis to death was 48 months.

Seven per cent of carcinomas of the thyroid are of the follicular and alveolar type. These patients usually appear with unilateral enlargement of the thyroid. In the absence of remote metastases,

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they present a clinical picture not unlike that seen with papillary tumors; they have an asymptomatic mass. These patients are often operated upon for adenoma of the thyroid. Only about 30 per cent of the surgically treated patients remain free of disease for five years. Of the 70 per cent that die, the interval of time from diagnosis to death is much less than for the papillary group.

TABLE I

Classification of Thyroid Carcinoma

1.	Papillary adenocarcinoma
2.	Follicular and alveolar adenocarcinoma
3.	Solid adenocarcinoma
4.	Spindle and giant cell adenocarcinoma
5.	Hürthle cell carcinoma
6.	Unclassified

Solid adenocarcinomas make up about 18 per cent of carcinomas of the thyroid. These tumors are generally more bulky than either of the preceding types. Bilobar thyroid enlargement is the rule. These patients on first examination often have cervical lymph node metastases, and remote metastases are not uncommon. When they are operated upon, 20 per cent of this group may expect to survive five years. Death due to recurrence may be expected to occur earlier than in either of the first two groups.

Patients with Hürthle cell carcinoma present physical findings similar to the follicular and alveolar cell carcinoma group. These tumors are encapsulated and may suggest to the examiner the presence of a small adenoma. When they are treated surgically, 35 per cent of them may expect survival without disease beyond five years. Those who die of recurrence often live as long as five years.

Spindle and giant cell carcinomas of the thyroid are usually seen in elderly patients. These tumors are often bulky, with a history of recent, rapid growth (fig. 5). There are no known five year survivals with this type of carcinoma of the thyroid. These patients usually have tracheal compression as the presenting symptom. The duration of life after diagnosis is less than one year.

From the foregoing descriptions, it may be seen that prognosis may be properly related to the histologic diagnosis. The histologic type and clinical stage are of importance in selecting a plan for surgical management. Radical thyroidectomy alone may be employed for a very small Hürthle cell carcinoma confined to the thyroid gland. Nothing less than a radical thyroidectomy and ipselateral radical neck dissection will suffice for a patient with a papillary

tumor which has metastasized to the cervical lymph nodes of one side of the neck.

Carcinomas of the thyroid gland differ from other carcinomas in their response to external irradiation. The more differentiated the thyroid tumor, the more sensitive it is to irradiation. Likewise, the more anaplastic thyroid tumors are less radiosensitive.

External irradiation has been ineffectual for all of the major histologic types except papillary adenocarcinoma. Prolonged, apparent arrest of papillary tumors has been observed when biopsy excision has been followed by irradiation. Recurrence at varying intervals of time occur after this program of treatment.

Routine postoperative irradiation is of questionable value. The authors feel that external irradiation has no place in the treatment of this disease unless it is demonstrably beyond the limits of surgical removal. Palliation, such as relief of pressure symptoms, may result from irradiation of bulky carcinomas of the thyroid.

Distinct clinical stages of carcinoma of the thyroid occur. The staging of carcinoma of the cervix and rectum, more than the histologic typing, is an estimation of the clinical problem. In table 2, staging of carcinoma of the thyroid is offered as a preliminary to a consideration of surgical approach.

TABLE II

Clinical Stages of Thyroid Carcinoma

Stage 1	
	a. Small primary carcinoma of the thyroid gland without clinical lymph node metastasis.
	b. Large primary carcinoma of the thyroid gland without clinical lymph node metastasis.
Stage 2	Carcinoma of the thyroid gland with unilateral lymph node metastasis.
Stage 3	Carcinoma of the thyroid gland with bilateral lymph node metastasis.
Stage 4	Carcinoma of the thyroid gland with distant metastasis, viz., pulmonary, skeletal, etc.

The type of surgery of the thyroid gland may establish the effectiveness of radioiodine. For this reason, all surgery of the thyroid will be referred to as radical thyroidectomy. By definition, this will infer that excision of thyroid tissue is performed so that thyroid remnants not exceeding 1.0 to 2.0 Gm. remain (figs. 10, 11).

The choice of surgery for Stage 1 will provide the major controversy. The differences of opinion will be whether radical thyroidectomy alone is to be done, or whether radical neck dissection

is to be added. The authors suggest that only small, ipselateral, pure papillary adenocarcinoma be treated by radical thyroidectomy alone. For a unilateral primary malignant lesion of the thyroid over 3.0 cm. in diameter, and for smaller primary malignant lesions, if the histologic type is other than papillary, elective, radical neck dissection is added to radical thyroidectomy. For a primary lesion involving both lobes, bilateral, elective, radical neck dissection is added. One of us (G.O.M.) has seen lymph nodes containing thyroid carcinoma removed from 2 patients subjected to elective radical neck dissection after carcinoma was found in the ipselateral thyroid lobe. These 2 patients did not have palpable cervical lymph nodes.

This surgical program may appear radical to many. Patients with small, unilobar thyroid carcinomas other than the papillary form, if treated by radical thyroidectomy alone will, in most cases, later have lymph node metastases. The same may be said for patients with large unilobar or bilobar carcinomas of the thyroid gland of all histologic types. The alternative to the suggested program for Stage 1 of this disease is to await the appearance of lymph node metastases. The known behavior of carcinoma of the thyroid suggests rejection of this alternative. The more radical surgical management is offered for improvement of the present inadequate results. The chief opportunity for the improvement of end results for carcinoma of the thyroid is the choice of surgical management for Stage 1.

The minimal surgical management of Stage 2 carcinomas of the thyroid requires radical thyroidectomy and ipselateral neck dissection (figs. 10, 11). The size of the primary lesion, its histology, and its location will determine whether to supplement the minimal surgery with a contralateral, elective, radical neck dissection. Since lymph node involvement usually exceeds that seen clinically, complete bloc dissection is the only surgical approach for metastases (figs. 2, 3).

The surgical management of Stage 3 carcinomas of the thyroid requires radical thyroidectomy and bilateral radical neck dissection. Consideration of the behavior of the histologic type is important before accepting the patient for surgery for this stage. Many of these patients can be greatly benefited by a radical surgical program.

Stage 4 carcinoma of the thyroid denotes the presence of remote metastases. There are reports of improvement and restoration of health by radioiodine therapy for this group. The success or failure of radioiodine therapy may be determined by the thyroid gland surgery. The role of thyroid surgery for a patient with remote metastases will be discussed under radioiodine therapy.

Radioiodine therapy is a recent contribution to the management of carcinomas of the thyroid. In 1940, Hamilton et al.[20] published an historic paper. Radioautographs of two carcinomas of the thyroid that failed to take up the isotope were shown. They concluded: "The failure of cancerous thyroid tissue to acquire appreciable quantities of radioiodine, as shown in these experiments, suggests the impracticability of therapeutic application of this radioelement in malignancies of the thyroid. It is possible that in other cases of carcinoma of the thyroid, radioiodine may be stored in the affected tissue in quantities sufficient for treatment." Since 1940, numerous investigators[12,14,15,16,18,32,33,36,44,48,49] have contributed to our knowledge of radioiodine. Some carcinomas of the thyroid initially concentrate radioiodine to therapeutic levels.

The therapeutic effect of radioiodine on carcinomas of the thyroid depends on ingestion by mouth, absorption into the blood stream, and tumor deposit.[37] After ingestion of radioiodine, absorption into the blood stream occurs rapidly. Most of the blood stream radioiodine is excreted by the urinary tract. Excretion is rapid and whole body irradiation is not significant. Repeated ingestions of radioiodine will depress elements of the hematopoietic system.

The amount of radioiodine deposited in carcinomas of the thyroid depicts therapeutic success or failure. A high-dose tumor irradiation effect is obtained if radioiodine concentration is adequate. This rarely happens initially. Radioiodine, not excreted, is primarily absorbed by normal thyroid tissue instead of by the tumor. The greater the differentiation and colloid element of the carcinoma, the better can it absorb radioiodine.

Destroying normal thyroid function may increase the capacity of the thyroid carcinoma to absorb the isotope. This may be done in three ways:

1. Surgical excision of normal thyroid, and accessible carcinoma, primary and metastatic.
2. Destruction of normal thyroid by radioiodine (referred to as "radio-elimination" of thyroid function by Paterson).[37]
3. Combination of (1) and (2).

Attempts to "radio-eliminate" thyroid function without preliminary radical thyroidectomy are rarely successful. Depression of the postsurgical thyroid remnant function by radioiodine is more often successful. Attempts at "radio-elimination" alone requires repeated ingestions of radioiodine, which may be dangerous. Con-

version of metastatic carcinoma of the thyroid to better absorb radioiodine may be accomplished by radical thyroidectomy alone.

For the above reasons, the choice of surgery to the thyroid gland with carcinoma is radical thyroidectomy. This will enhance future radioiodine effect if recurrence appears. This is not to infer that radical neck dissection is not often an essential supplement. Removal of accessible metastases may increase the deposition of radioiodine in distant metastases. Seidlin[44] is of the opinion that most tumors will, after normal thyroid destruction, absorb radioiodine. A myxedematous state is desired for a beneficial radioiodine effect. Propylthiouracil may be given over a long period of time. Intensive administration of thyrotropic pituitary hormone prior to radioiodine may be helpful. External irradiation to the metastases has been suggested to alter its radioiodine capacity. It is no longer true that all patients with disseminated carcinoma of the thyroid may expect only temporary palliation.

It becomes increasingly evident that we must vary our management of carcinoma of the thyroid. Three case reports are offered:

CASE 1. B. G., a 19 year old unmarried female, was first seen in November 1948. In 1935, at the age of 6 years, a mass had appeared in her right neck. A tonsillectomy had no effect on the neck tumor. Since no apparent increase in size occurred at that time, she was observed. At the age of 13 years, shortly after the onset of menses, an increase in size of the neck tumor was observed. At that time a roentgenogram of the chest revealed a substernal mass 8.0 cm. in diameter. Her thyroid gland was described as not enlarged at that time. At the age of 15 years she had numerous bilateral neck nodes and an enlarged thyroid gland. A biopsy specimen of a neck node was reported to be "papillary adenocarcinoma of the thyroid."

At the age of 15 years, a subtotal thyroidectomy was done in another city. A decision was made to treat the metastatic carcinoma of the cervical lymph nodes with roentgenotherapy.

Roentgenotherapy at intervals was administered for four years before she was seen by one of us (G.O.M.) at which time she was 19 years of age (fig. 1). She had a nodular mass of lymph nodes, quite large, extending from the clavicle to the mastoid process bilaterally. The skin of the neck revealed marked tanning from irradiation. She and her radiotherapist stated that for the first two years marked regression of her neck disease followed roentgenotherapy. Not only was recent roentgenotherapy ineffective, but her skin did not suggest additional tolerance to this agent.

A roentgenogram of her chest was taken and compared to the film taken six years before. There was no demonstrable roentgenographic change in the substernal mass during the six-year period. Skeletal disease was not demonstrated. Radioiodine studies were not available for our use at that time.

In December 1948 a right radical neck dissection was done (fig. 2). Remnants of thyroid tissue containing carcinoma were removed at that time. In March 1949 a left radical neck dissection was done (fig. 3). Internal jugular veins, sternocleidomastoid muscles, submaxillary glands and contiguous lymph-

Fig. 1. B. G., case 1. Preoperative photograph showing lateral neck masses of metastatic thyroid carcinoma. Note the irradiation telangiectasis of the skin over the upper sternum.

Fig. 2. Posterior view of right radical neck dissection specimen of B. G., case 1. Many large lymph nodes, all showing metastatic thyroid carcinoma, have been sectioned to show their size.

Fig. 3. Anterior view of left radical neck dissection specimen of B. G., case 1. The bulk of metastases to lymph nodes is equivalent to that of the opposite side (fig. 2).

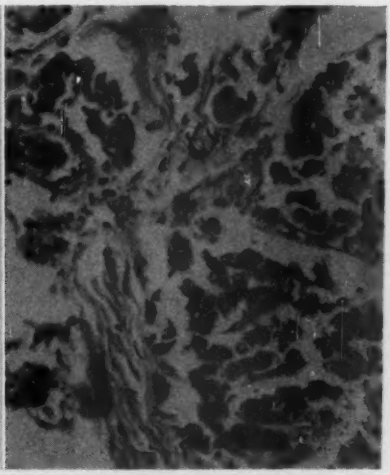

Fig. 4. Photomicrograph of metastatic papillary adenocarcinoma of the thyroid taken from a lymph node from the specimen shown (fig. 2).

atic and adipose tissues were removed on each side en bloc. In October 1949 the mediastinum was explored through a right lateral thoracotomy. Many bulky lymph nodes replaced by carcinoma of the thyroid were removed. Radioiodine studies done in September 1950 showed no radioactive concentration in the neck or mediastinum. The patient has been seen at intervals and on June 25, 1951, she still showed no clinical or radiographic evidence of recurrent disease. She has worked for over a year as a stenographer and was married in March 1951.

Comment: The clinical course of this tumor is that of a pure papillary adenocarcinoma. In keeping with surgical principles for malignant disease, her best chance of complete tumor removal would have been by a radical surgical approach at an early age. One might compare some of the papillary adenocarcinomas of the thyroid to some of the basal cell carcinomas of the skin of the face. They may go for years with no treatment and little change, and eventually present an almost impossible problem. If this girl develops recurrence, radioiodine therapy will be considered. If she can be made myxedematous, her tumor may better concentrate radioiodine. She is not now myxedematous by clinical or laboratory standards.

CASE 2. O. J., a 74 year old white female, weighing 215 pounds, was first seen in the University of Kansas Hospital in September 1950. She complained of difficulty in breathing and swallowing for three weeks, and a mass in her

Fig. 5. O. J., case 2. This thyroid mass reportedly reached this size in six weeks. The histologic type is spindle and giant cell adenocarcinoma of the thyroid.

Fig. 6. Bulky mass excised from O. J., figure 5, for relief of tracheal compression only.

neck for six weeks. Her physician stated that she had minimal thyroid enlargement six weeks prior to hospital admission. Upon admission, the thyroid mass measured 12.0 cm. in diameter and elevated the skin 7.0 cm. (fig. 5). Numer-

ous palpable nodes were present in both sides of the neck. She had moderate stridor. A roentgenogram of her chest was negative. Other findings on the physical examination were negative, except for obesity, mild hypertension, and an umbilical hernia.

Radioiodine studies showed that the tumor failed to concentrate therapeutic amounts of the isotope.

A lymph node biopsy specimen revealed a highly anaplastic carcinoma, spindle and giant cell in type. For this reason, any thought of extensive surgery was rejected for this patient. Roentgenotherapy was expected to be ineffectual. The patient presented a picture of impending tracheal obstruction; tracheostomy alone would be difficult due to the thickness of the tumor mass. In October 1950 the bulk of the thyroid mass was removed (fig. 6). No effort was made to do any lymph node dissection. A tracheostomy was performed. The patient was improved and grateful after surgery. Postoperative external roentgenotherapy was administered. The cervical lymph node metastases enlarged noticeably from week to week during and after completion of her roentgenotherapy.

The patient's condition grew steadily worse and she died in December 1950. An autopsy revealed extensive mediastinal, subpleural, and retroperitoneal metastases.

Comment: Spindle and giant cell carcinoma of the thyroid is more often seen in the sixth to eighth decades of life. This type of neoplasm is not often seen in young females whose carcinomas are predominantly papillary in type.

The lack of response to external irradiation and the inability of the tumor to pick up radioiodine is characteristic of this type of carcinoma. The history of rapid, almost improbable, rate of growth is characteristic of spindle and giant cell adenocarcinoma of the thyroid.

Palliative measures for relief of obstruction are often necessary for this group of patients. Actually, many patients may have their lives extended in comfort many months to over a year by relieving their tracheal obstruction. Roentgenotherapy for this histologic type of carcinoma of the thyroid is of no benefit.

CASE 3. A. L., a 4½ year old white girl was first seen in January 1951. Her physician had noted a mass in her right neck in November 1950. A lymph node biopsy section taken in January 1951 was reported as papillary adenocarcinoma of the thyroid, grade II. When first seen by us, the patient had bilateral, large, matted, lymph node masses extending from the clavicle to the mandible (fig. 7). The thyroid was two times normal size. A chest roentgenogram of the chest was negative. A tracer dose of radioiodine showed virtually no uptake in the thyroid bed or the lymph node metastases. On Jan. 18, 1951, a radical thyroidectomy and right radical neck dissection was done (fig. 8). Both recurrent laryngeal nerves were isolated and traced 3.0 cm. before their entrance into the larynx. The anterior two-thirds of the larynx and trachea were skeletonized. The amount of resected thyroid tissue gave great concern over possible interference with parathyroid function. A tracheostomy was not necessary. Her postoperative course was uneventful and she was discharged on the tenth postoperative day.

The patient was readmitted to the hospital for left radical neck dissection which was done Feb. 23, 1951 (fig. 9). On Feb. 22, 1951, a repeat tracer dose of radioiodine was given to compare the isotope concentration in the

Fig. 7. Front (a) and side (b) view of A. L., case 3, taken before definitive surgery.

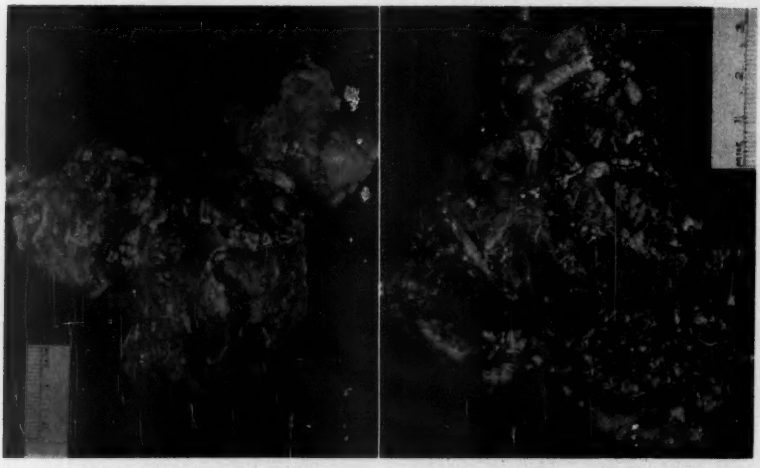

Fig. 8. Right radical neck dissection surgical specimen of A. L., case 3 (fig. 7).

Fig. 9. Left radical neck dissection surgical specimen of A. L., case 3 (fig. 7).

metastases in the left neck with what it had been before radical thyroidectomy. There was greatly increased pick-up of radioiodine by the metastatic disease of the left neck lymph nodes. Table III shows the determination made before and after radical thyroidectomy. On March 2, 1951, she received a thera-

peutic dose of 40 mc. (Oak Ridge Standard) of radioiodine (I^{131}). Her thyroid function on July 6, 1951, showed markedly decreased thyroid hormone output. The therapeutic dose of radioiodine, in addition to depressing residual thyroid remnant function, should deposit in any residual carcinoma of the

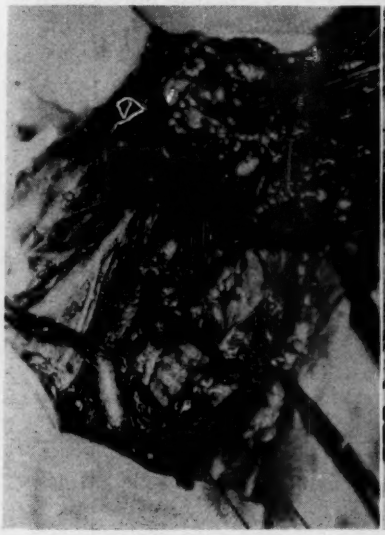

Fig. 10. S. W. Operative field after completion of radical thyroidectomy and the lower half of the radical neck dissection for a patient of 65 yrs. with papillary adenocarcinoma of the thyroid and metastases to lateral neck lymph nodes. The common carotid artery is retracted laterally to show the recurrent laryngeal nerve. Note the size of thyroid remnants.

Fig. 11. S. W. Operative field at completion of radical thyroidectomy and radical neck dissection shown in fig. 10. Note small thyroid remnants; the recurrent laryngeal, vagus, cervical, sympathetic, phrenic, and hypoglossal nerves are dissected clean and intact.

thyroid. She is clinically free of disease. There is the additional task in this child of avoiding cretinism which should be no problem unless she develops recurrence; in that case, for radioiodine effect a myxedematous state is desired.

Comment: This girl's surgical treatment was planned to create tumor affinity for radioiodine if she develops metastases. In addition to removal of carcinoma, it was hoped surgery would change the tumor affinity for radioiodine. Based on the radioiodine uptake studies, that change occurred. The increased radioiodine concentration in the metastases to lymph nodes of the left neck was well beyond the limits of laboratory error (table III). A potential therapeutic affinity of this tumor for radioiodine has been established by the surgical treatment.

Conclusions

The surgical approach for treatment of carcinoma of the thyroid gland must be individualized. The variations in behavior of the main histologic types of carcinoma of the thyroid are discussed.

TABLE III

*Tissue Radioiodine Activity Before and After Radical Thyroidectomy**

Tissue	*Before Radical Thyroidectomy* C.P.M./Gm. (wet weight)	*After Radical Thyroidectomy* C.P.M./Gm. (wet weight)
Tumor Section No. 1	720	
Tumor Section No. 2	670	
Lymph Node Metastasis No. 1	780	
Lymph Node Metastasis No. 2		6,428
Lymph Node Metastasis No. 3		4,710
Lymph Node Metastasis No. 4		5,180
Muscle	195	180
Skin	120	125

*Counts are corrected for decay to the time of radioiodine administration. Radioactivity is assayed by the silver iodine method using a Tracerlab 64th scaler and an open thin window TG-2 Geiger-Mueller tube.[23]

The therapeutic role of radioiodine for carcinoma of the thyroid may be greater than the initial studies of a patient may suggest. Surgery should be planned for the possible conversion of carcinoma of the thyroid into a radioiodine-concentrating tumor. Limited surgery and external irradiation are not considered a part of definitive treatment for carcinoma of the thyroid. Carcinoma of the thyroid is primarily, though not entirely, a surgical disease.

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CONGENITAL TRACHEO-ESOPHAGEAL FISTULA—NASOGASTRIC POLYETHYLENE TUBE IN LIEU OF GASTROSTOMY*

Case Report

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IT IS generally believed that an indwelling postoperative rubber nasogastric tube following the repair of a congenital tracheo-esophageal fistula is conducive to ulceration at the suture line, increased incidence of immediate leak, and eventual stenosis, although some surgeons still employ this technic. It has been customary to perform a gastrostomy for feeding purposes either at the same time that the tracheo-esophageal fistula was repaired or within a few days thereafter. The undesirability of adding an additional transperitoneal operative procedure to the severely ill newborn infant is obvious; yet the problem of early alimentation without producing undue trauma of the suture line remains.

The use of indwelling polyethylene tubing for the nasogastric feeding of small infants has received some attention in recent pediatric literature. Royce, Tepper, Watson, and Day[1] reported on the use of the tubing in premature infants, leaving it in place from 7 to 49 days. Only 2 babies in the 30 observed at autopsy showed esophageal ulceration, which is a lower incidence of ulceration than has been found in a study of routine autopsies[2] of premature infants without the use of nasogastric tubing of any type. Andrews and Traisman[3] have used plastic tubing successfully in the feeding of infants with marked generalized debility and cachexia.

From these observations it was reasoned that the resutured esophagus of the newborn infant with tracheo-esophageal fistula should stand the presence of nasogastric polyethylene tubing for a considerable period of time without severe tissue reaction or ulceration. When a case of tracheo-esophageal fistula presented itself to the authors, we felt justified in substituting the indwelling nasogastric plastic tubing for the usual gastrostomy and we present the following case report:

CASE REPORT

W. H., a male infant weighing 6 pounds and 7 ounces, was born on Oct. 19, 1951, at St. Mary's Hospital. When feedings were begun, it was appar-

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ently impossible for the child to swallow and every attempt resulted in regurgitation and cyanotic episodes. On the infant's third day of life a few rales were heard at both bases, and a roentgenogram indicated slight bilateral basilar congestion of the lungs or pneumonitis. Air was present in the stomach and intestinal tract, and lipiodol swallow revealed a blind upper pouch of esophagus. A diagnosis of congenital tracheo-esophageal fistula with patent distal segment was made. The child was properly hydrated and antibiotics were begun.

On October 23, under endotracheal anesthesia, a right transpleural thoracotomy was carried out; the fistula was closed, and a small hypoplastic distal esophageal segment was sutured with interrupted silk (five O) to a dilated thickened upper pouch. Before the anastomatic line was completed, a polyethylene tube, size 160, was inserted into the esophagus through the child's nose and was threaded down the distal esophageal segment well into the stomach. The child's chest was then closed, the lung expanded, and the postoperative course was essentially uneventful.

Nasogastric feeling by means of the polyethylene tube was begun the morning after surgery and parenteral alimentation was stopped. The nasal end of the tube was plugged in order to prevent digested material from regurgitating into the tube and clogging its lumen. The child's hands were immobilized to prevent his catching his fingers in the tube and withdrawing it. The plan was to keep the tube in place 10 to 14 days, but unfortunately the infant's arm got loose and the tubing was accidentally pulled out on the sixth postoperative day. Oral feeding was started shortly thereafter and the child's subsequent postoperative course has been completely uneventful. He is now eating well and gaining weight.

Comment

It has always seemed to us that the presence of a firm rubber catheter in the esophageal lumen, particularly when the anastomotic site is small as in this instance, constitutes a definite invitation to pressure ulceration when the anastomosis undergoes the inevitable early postoperative edema. Furthermore, the policy of early oral feeding following esophago-esophagostomy in these newborn infants would hardly seem to be the logical procedure, as it is in the adult patient, because of the relatively insecure anastomosis which one often has to be satisfied with in these tiny infants. The advantage, however, of not adding the additional transperitoneal procedure of gastrostomy is apparent, and yet the virtual impossibility of maintaining an infant's nutritional status on parenteral alimentation for any period of time is known to all. It would seem that the use of the small nasogastric polyethylene tubing in a manner such as the one employed in this case might answer the feeding problem without being subject to the disadvantages of any of the above methods.

The caliber of the polyethylene tubing to use and the length of time to keep it in place are questions not settled to date. In retrospect, it would seem that a smaller polyethylene tube, size 90, might

be somewhat more advisable than the size used in this case, although at the time of surgery the tube certainly fit very loosely through the anastomotic line, even with a distal esophagus which was quite hypoplastic. We believe that, in the average case, such a size of polyethylene tubing would produce little, if any, irritation of the esophagus. Small size polyethylene tubing presents difficulty in its introduction into the esophagus, particularly under anesthesia. It can, however, be loosely attached to the trailing end of a very small firm rubber catheter which can then be brought out through the anastomotic line at the time of closure of the esophagus with the chest open. The polyethylene tube is threaded down the distal esophagus into the stomach after the small rubber tube has been removed. This was the technic employed in this patient.

Summary and Conclusions

The disadvantages of the various technics of postoperative alimentation following repair of congenital tracheo-esophageal fistula are enumerated.

The successful use of nasogastric polyethylene tubing over prolonged periods of time in newborn and even in premature infants without evidence of significant esophagitis and ulceration is noted.

The use of an indwelling nasogastric polyethylene tube for purposes of postoperative feeding following the repair of a tracheo-esophageal fistula in a newborn infant is suggested and a case report is given.

Preliminary observation indicates that an indwelling nasogastric polyethylene tube of small size constitutes a satisfactory method of postoperative feeding following repair of congenital tracheo-esophageal fistula.

Further trial with this method seems to be justified.

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FAT EMBOLISM IN NEUROSURGERY*

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GROSSKLOSS,[1] Scuderi,[2] and Warthin[3] have reviewed extensively the literature on fat embolism. They agree that the concept of this condition originated from Lower's experiments with intravenous milk in 1669, and was extended by the researches of Magendie and Virchow with intravenous oil during the nineteenth century. During the same century, according to these authors, fatty emboli were observed in the eye by Müller, in the capillaries of the brain by Cohn, and in the pulmonary vessels by Zenker. The evolution of theories concerning fat embolism has been slow, the literature voluminous, and much remains in dispute.

Emboli of the fat produce an impediment to the flow of blood by temporary occlusion of the smaller ramifications of the vascular tree with oily globules. The physical ability of this viscid liquid substance to accommodate itself to, and eventually to pass, the small calibers of the capillary barriers was recounted by Scuderi.[4] Under these circumstances a large functional alteration is possible without appreciable damage. Hurst and Cooke[5] were able to produce experimentally small vessel obstruction with mayonnaise without appreciable residual parenchymal damage. Injury occurred only when many adjacent capillaries were blocked, or rather large vessels were occluded by large fat globules and even then the parenchymal damage was minimal. Newman,[6] in tabulating the diagnostic features of 7 cases, reaffirmed an alternate elevation and depression of the conscious state. The ability of fat globules to pass the capillary barrier and produce repeated showers of emboli permits clinical fluctuations.

The origin of fat emboli is a subject of considerable dispute. Bone marrow, depot fat, and the fat physiologically present in the blood stream are three sources generally considered. Bone marrow, however, is the more favored of these. Newman had a very fundamental basis for this belief in the work of Busch done in 1866. Busch injected vermilion into the medulla of a long bone, and then fractured it. Moments later the characteristically stained fat was seen in the pulmonary vessels. Baronofsky[7] and Friesen[8] and their coworkers have more recently been able to demonstrate repeatedly the embolism of fat by trauma to the long bones and the medullary cavity of experimental animals. Whitson,[9] on the other hand, in a recent criticism of this disorder, called attention to the infrequent

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occurrence of fat embolism following orthopedic procedures, and denounced the concept. Lehman and Moore[10] also estimated that only 65 cc. of fat was present in the marrow cavity of an adult femur. By computing the lethal dose of intravenous neutral fat in dogs, they estimated that 90 to 120 cc. would be required for lethal effects in an average adult human.

The increased use of radiopaque oils in diagnostic procedures has led to occasional accidental embolism. Grossmann[11] reported 2 cases of embolism following uterosalpingography, supported by roentgenographic evidence of both uterine intravasation and pulmonary emboli. Mild symptoms developed in the first case two days after the test. In the second case, the symptoms were immediate and serious. Both cases recovered. The same author found instances of lethal effects in the literature, when as much as 30 to 40 cc. of iodized oil was inadvertently given intravenously in the course of a subcutaneous injection, and when as little as 8 cc. of lipiodol was intravasated in uterosalpingography.

Depot fat comprises an extensive reservoir in the subcutaneous and connective tissues, and is frequently underemphasized in the evaluation of traumatic cases. Robinson[12] reported 2 cases of fatty embolism following laparotomy in obese individuals. Carter[13] and co-authors likewise reported 2 confirmed and 5 suspected cases of the same condition following thoracoplasty. These authors implicated trauma to depot fat, as well as bone involved by rib resection, in the etiology. Oil was introduced intramuscularly by Bisgard and Baker,[14] and observed in the phagocytic cells of the lungs 48 hours later.

A new source was suggested when fatty emboli were found in some systematic diseases, poisons, burns, and conditions not ordinarily associated with physical violence as it is considered in this disorder. Lehman and Moore demonstrated the in vitro destruction of fat emulsions with products of tissue decomposition, fat solvents, and other substances. Fat physiologically present in the blood could provide 105 cc. for emboli, according to their calculations. Despite this inference, the in vivo extension of their studies with products of tissue decomposition proved disappointing. They successfully produced fat emboli, however, by feeding their experimental animals a high fat meal and administering ether. Lichtenstein[15] later reported the necropsy study of a case of fat embolism which followed ether anesthesia, and cautioned against the ingestion of fats in the preanesthetic period.

Other authors have provided interesting adjuncts to our thinking on this subject. Scuderi[16] repeated modified experiments of previous

investigators, and showed that a tolerance to fat could be developed by slowly increasing the amount administered. By transfusion studies, he further demonstrated that this was not a blood-borne factor transferable from animal to animal. Hirsch[17] studied the reactivity of tissues to fat from a very general viewpoint. He considered fat to be inert until chemically altered, whereupon the reaction depended upon the changed properties. This gave rise to the thought that local alteration of embolic fat, by hydrolysis for instance, might aggravate the toxicity.

The signs and symptoms of fat embolism are related to the organ systems involved. The most disturbing of these are usually cerebral, although the pulmonary ones are prominent. Emboli to the coronary vessels, while perhaps overshadowed in the total clinical picture, must receive consideration if cardiac arrhythmias, cardiac standstill, or electrocardiographic changes appear. It is interesting that the kidneys may show many emboli pathologically, escape unscathed clinically, and be involved in the excretion of the fat physiologically (Scuderi).[18]

Laboratory support of the fat emboli syndrome may be obtained by the demonstration of fat in the urine, sputum, blood, biopsy specimen of skin petechiae, and material obtained by lung puncture (Newman). Scuderi introduced the "sizzle test," which is distinguished by its simplicity of performance. He showed that the presence of very small quantities of fat in the urine would sizzle in an open flame.

Roentgenograms of the chest are useful in the diagnosis of this condition. Scuderi produced fatty emboli in dogs and demonstrated a clouding or haziness in the chest roentgenograms, which persisted five to seven days. Clinically the condition appears as patches of increased density in the lung fields. Perhaps, when incompletely aware of the problem, the roentgenologist may interpret this as bronchopneumonia.

Many pitfalls arise in the clinical interpretation and application of laboratory tests. This may be due in part to the physical properties of the fat, the technique of the test, or even to the nature of the disease. Scuderi emphasized that fat may float to the surface of urine and be retained in the bladder, only to be lost at an inopportune moment or remain unsuspected. Oil may also be introduced by an oversight in lubrication practices while obtaining the specimen, and care must be exercised that fat solvents are not used in the preparation of biopsy material. Chest roentgenograms, like laboratory tests, present problems that are not easily surmounted. Portable technics are of limited value and the condition or cooperation of the patient may preclude diagnostically adequate films.

Treatment, other than general supportive measures, leaves much to be desired. In general, careful handling of the patient, interruption of the lymphatic or venous drainage by mechanical or surgical procedures, and the systemic administration of drugs to saponify, emulsify, change the solubility of the fat, or increase the metabolism of it have been proposed. Ligation of the vena profunda and femoral vein has been used by recent authors with questionable benefit. Sodium desoxycholate and ether have been employed with little more than amelioration of symptoms. Wilson and Salisbury,[19] impressed by the work of Lombrose, in which insulin was shown to be essential to the metabolism of fat in the liver, gave five units of insulin hourly with questionable results. Bisgard and Baker, Scuderi, and others have investigated similar therapeutic measures in experimental animals. They were able to reduce the grade of fatty embolism, but could not prevent it.

I THE INJURY INVOLVED
- a) Fracture of bone(s)...21
- b) Surface contusions....12
- c) A viscus.....4

II PREVAILING SYMPTOMS
- a) Premonitory cerebral signs and symptoms....16
- b) Found in coma or stupor.....5
- c) Altered conscious state developed 21
- d) Respiratory symptoms evident 17

III VITAL SIGNS

	Temp.	Pulse	Respirations	B. P.
a) Recorded in	14 cases	14 cases	10 cases	11 cases
b) Over	101 in 10	120 in 12	24 in 10	100 systolic in 9

IV PETECHIAL HEMORRHAGE
- a) Skin and conjunctiva...6
- b) Fundi.....7

V LABORATORY PROOF OF FAT IN:
a) Urine....5 b) Sputum....2 c) Biopsy...1

VI SPINAL FLUID PRESSURE
Measured in 11; normal in 11

VII MORTALITY: 15
In less than 24 hrs...6; In 2 to 10 days..9

VIII RECOVERED: 9 Recovery time 5 to 14 days.

Following the pattern of Newman, who summarized the clinical aspects of 7 cases in chart form, the following 3 cases and 19 additional cases from the recent literature[19,20,21,22,23,24,25,26,27] were surveyed for a clinical pattern. The statistics from these cases are presented in table 1, and summary of the clinical features in table 2.

CASE 1. G. E. A., a 23 year old patrolman, was admitted on the afternoon of Jan. 26, 1951, as a transfer from another hospital.

He had sustained multiple soft tissue injuries and fractures (left femur, left acetabulum, and left second metatarsal) without loss of consciousness in an automobile accident on the night of Jan. 24, 1951. Approximately 36 hours later he developed a generalized convulsion and rapidly lost consciousness.

SYNDROME OF FAT EMBOLISM

I INJURY TO BONE AND/OR SOFT TISSUE

II LUCID INTERVAL
Usually 12 to 48 hours, occasionally much longer

III PREMONITORY CEREBRAL SIGNS AND SYMPTOMS
Anxiety, apprehension, agitation, irritability, confusion, delerium and convulsions may herald onset. Temperature is usually 101 to 103. Neurological signs and pupillary changes, occasionally falsely focal, are not infrequent.

IV ALTERED CONSCIOUS STATE
Drowsiness, clouding of sensorium, progressing to stupor usually develops with cerebral symptoms. Alternate elevations and depressions may occur. Coma may be the prominent feature if symptoms develop rapidly.

V RESPIRATORY SYMPTOMS AND SIGNS
Oppressive chest distress, shortness of breath, hyperpnea, dyspnea, cough, frothing, blood tinged sputum and chest rales are frequent. Chest x-rays may reveal patchy consolidation, often interpreted as bronchopneumonia. Pulse is usually 120 to 140.

VI PETECHIAL HEMORRHAGES
Particularly evident about base of neck, conjunctiva and fundi.

The physical examination revealed a critically ill, comatose individual, with a mild right hemiparesis and perhaps aphasia. The respirations were 24 and his pulse 136 per minute, blood pressure 130/70, and rectal temperature 100.4 F.

Bilateral trephinations were immediately performed with negative results. A Steinman pin was simultaneously inserted into the left tibia for traction purposes. A lumbar puncture was performed postoperatively. The pressure was normal and the fluid clear. A very careful scrutiny of the fundi revealed a small hemorrhagic area in the paramacular area of the right eye. On the following day the pathologic condition was more extensive and the consulting ophthalmologist reported multiple small patches of retinal edema and hemorrhage consistent with fat emboli.

The patient remained in a critical condition, with occasional periods of Cheyne-Stokes breathing. The pulse and respirations became more rapid, and the temperature rose to 102 F. On Jan. 30, 1951, a ureteral catheter was introduced into the vicinity of the left stellate ganglion (figs. 1, 2). An intermittent procaine block was then produced, using the patient's response as a guide to the interval. Approximately 10 cc. of 1 per cent procaine was administered at two-hour intervals. An immediate improvement in his general condition, neurological status, and conscious state became apparent. He responded to his mother's voice, simple commands, and made a feeble effort to speak. After a short period the pulse, respiration, and temperature resumed a near normal level. This was a remarkable change in comparison with his previous state, but still remote from the alert response to be desired. The

effect was not permanent and lasting. Each injection of procaine produced similar beneficial results.

On Feb. 5, 1951, the patient inadvertently displaced the catheter. Although some clouding of the sensorium persisted, he was sufficiently improved that replacement was not necessary.

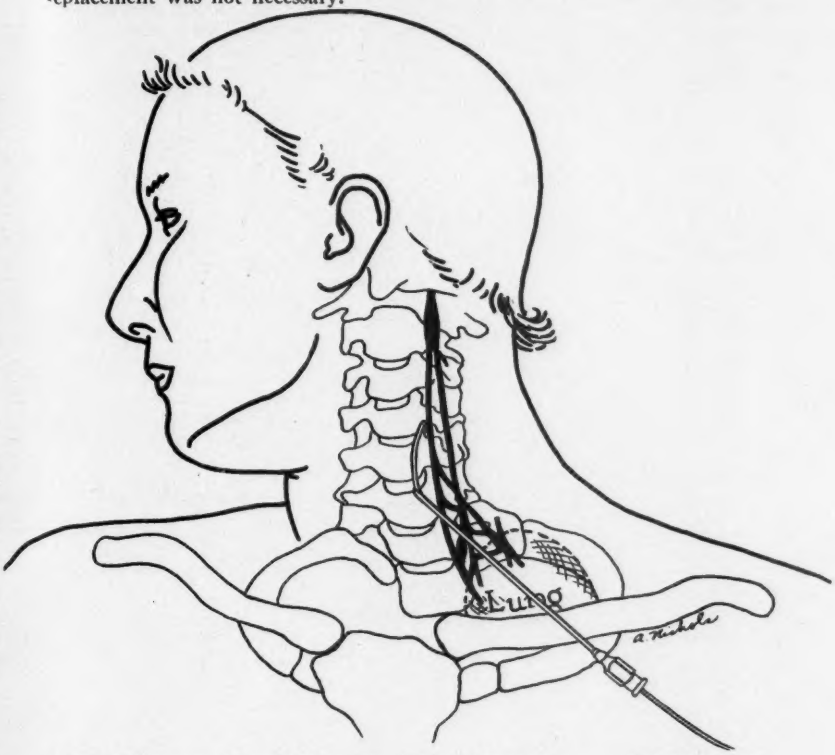

Fig. 1. Diagram of cervical sympathetic block, illustrating use of Touhey needle to introduce ureteral catheter.

The patient developed symptoms of a left hydropneumothorax which required aspiration on Feb. 9, 1951. Following a prompt recovery from his chest complication, his hospital course was uneventful. He was discharged March 15, 1951.

CASE 2. J. C., a 38 year old male, was admitted to the hospital emergency room immediately following an automobile accident on May 10, 1951. Multiple soft tissue injuries and a left intertrochanteric fracture were sustained. The most serious injury was in the neck. The trachea, larynx, and contiguous structures were displaced to the right and possibly fractured. Evidence of tracheal obstruction was present. A 4 by 7 cm. avulsion injury involved the superficial tissues of the left face and temple. The patient was conscious, apprehensive, and appeared to comprehend, but could not speak due to discomfort in the effort. The pupils were widely dilated and fixed. The fundi were normal. Clinical shock was present.

A tracheostomy was immediately performed. Transfusions of plasma and blood were administered. The avulsion injury was cleansed and sutured. The intertrochanteric fracture was incomplete and required no special treatment.

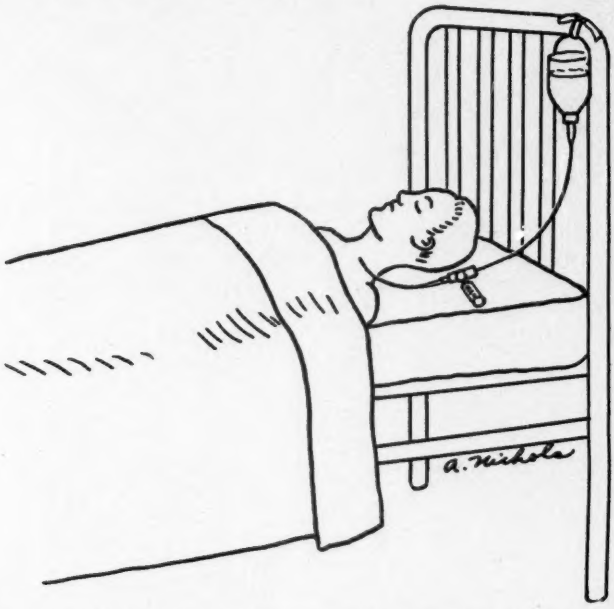

Fig. 2. Illustration of technic of intermittent procaine block in cervical region.

During the initial three days of hospitalization, the patient developed an oliguria. The nonprotein-nitrogen rose to 150 mg. per hundred grams, and the createnine to 5.4 mg. Upon the advice of a urologist, he was managed as a lower nephron nephrosis restricting the fluids to the tolerance of his renal threshold. His temperature during this period ranged from 100 to 101 F., the respirations were 24 to 28, and the pulse was 90 to 120 per minute. The blood pressure was stable. A roentgenogram of the chest revealed diffuse clouding over the entire right lung field and base of the left lung.

On May 13, 1951, he developed evidence of a right hemothorax, which required repeated aspirations.

The fundi were normal on May 15, 1951. On May 18, without other cerebral or respiratory symptoms, large patches of retinal edema and hemorrhage became apparent, particularly in the macular and paramacular areas. The pupils were still widely dilated and reacted almost imperceptibly to light. A puzzling type of amblyopia became apparent during the initial hospital period, but the gross visual acuity remained unchanged. The ophthalmologist described this retinopathy as a vascular lesion, most likely due to fat embolism. This condition improved slowly.

The patient's tracheostomy tube was removed on May 25, 1951. He signed a hospital release on June 3, declining further therapy.

CASE 3. W. C., a 24 year old male, was injured in an automobile accident at 1:30 p.m. on June 29, 1951. A compound fracture of the left tibia and fibula, comminuted fracture of the right femur, and contusions were sustained. There was no alteration of consciousness.

Steinman pins were inserted into the distal right femur and left os calcis, employing local anesthesia. The compound injury was cleansed, debrided, and sutured. Prophylactic tetanus antitoxin was given.

Around 2:30 on the afternoon of June 30, 1951, the patient complained: "My chest feels like it is caved in." Thereafter he became restless, agitated, irrational, and incontinent of urine. By 6:00 p.m. on the same day, he could not be aroused. The blood pressure was 115/80, the respirations 24 and the pulse 120 per minute.

The following morning he was seen in neurosurgical consultation. The pupils were equal and reacted to light. The fundi were normal. He responded readily to painful stimuli, moving all extremities with equal ability. A left facial paresis and aphasia was suspected, but not established. Bilateral Babinski responses were elicited.

During the afternoon of July 2, 1951, petechiae appeared over the trunk and in the conjunctivae. The consulting ophthalmologist reported a single small paramacular hemorrhage in the right eye on the same day. A new hemorrhage was reported in the left eye on July 5, 1951. The skin petechiae faded on July 6, 1951.

The course of the patient exhibited alternate elevations and depressions of the conscious state. The pulse and respiratory rates were elevated. The temperature was 100 F. at the onset, and normal thereafter. His cerebral symptoms persisted in fluctuating degrees through July 10, 1951, subsiding thereafter.

An open reduction of the right femur was performed on July 20, 1951. The remainder of his hospital course was uncomplicated. He was dismissed on Sept. 25, 1951.

DISCUSSION

The 3 cases presented embolic phenomena which followed trauma. Fat was never demonstrated by laboratory methods. Nevertheless, a clinical diagnosis was considered tenable. A review of table 2 suggests that the disease is encountered much more frequently than laboratory tests substantiate it to be. To whatever extent one may question the validity of the figures in this table, or the avidity with which laboratory diagnosis is pursued, most clinical investigators have encountered difficulty in the laboratory methods of appraisal. Such laboratory methods fail in their purpose when the technical aspects become too difficult. A clinical approach under such circumstances might prove more practical.

In the 3 cases here recorded, considerable diagnostic significance was attached to the petechiae, particularly the retinal hemorrhages. The fundi were repeatedly examined by members of the departments of neurosurgery and ophthalmology. All agreed the retinopathy was embolic, and fat appeared to be the only feasible cause.

The retinopathy in the first case was observed as it developed and waned. Initially the hemorrhage and edema were small, sparse, and difficult to find; then they enlarged, multiplied and became obvious. The retinal changes developed in the second case so suddenly and unexpectedly that they were extensive on the initial examination. Only solitary hemorrhages, on the other hand, were observed in the last case.

Pupillary changes, such as anisocoria, or unilateral dilatation with light-rigidity, have been described in fat embolism by other authors. Bilaterally dilated, light-rigid pupils, when encountered in neurosurgery, are usually associated with profound alterations of the consciousness, and are indicative of an ominous prognosis. This finding in case 2 occurred in a conscious individual, which probably mitigated its prognostic significance. The explanation of the associated amblyopia remains a matter of conjecture. Since amblyopia appeared with the pupillary changes and in the absence of retinopathy, embolic involvement of the optic pathways may merely be surmised.

The response of the first case to unilateral stellate ganglion block is of interest. The response was not dramatic, but apparent to all concerned. The significance of such amelioration upon the eventual mortality remains to be evaluated.

SUMMARY

A brief résumé of the literature on fat embolism is given. Three case summaries are presented. These and 19 additional cases from the recent literature are reviewed and their clinical aspects summarized. Interesting neurological features are discussed. The ameliorating effect of stellate ganglion block upon the course of the disease is suggested.

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PERSISTENT ALBUMINURIA FOLLOWING PREECLAMPSIA*

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THIS presentation is based upon the study of a patient having marked and persistent albuminuria for at least five years following two episodes of preeclampsia, who has no other evidence of renal disease, has normal liver function and has no hypertension.

It is an accepted fact that small amounts of protein are normally filtered by the glomerulus and reabsorbed in the proximal tubule[1] but the appearance of over 0.2 per cent of albumin in the urine usually indicates the presence of serious renal disease.[2]

Although reports of the after effects of eclampsia and preeclampsia are not entirely in agreement, from the early report of Von Koblanck[3] in 1894 to that of Page and Cox[4] in 1938, it is apparent that a much higher per cent of women who have had eclampsia or preeclampsia develop persistent albuminuria, usually with associated hypertension, than do parous women who did not experience this disease. The most satisfactory explanation of albuminuria in such a condition is that there is permanent damage to the glomerular membrane. Page and Cox reported 7 women known to have had preeclampsia who died of other causes later, all of whom had thickening of the capillary basement membranes.

CASE PRESENTATION

H. S., a 42 year old white female, had moderate preeclampsia for the last trimester of her first pregnancy in 1942 but had a full term delivery and apparently was well following delivery. Her symptoms and signs were: edema, hypertension and albuminuria. In 1946 she developed edema, hypertension and albuminuria after three to four months of her second pregnancy (she was not certain exactly how long she had been pregnant) and had a therapeutic abortion. (No exact data on these hospitalizations are available.) Following the abortion she was symptomatically well and was told that she had no hypertension or albuminuria.

She was first seen in our hospital in September 1948 with the complaint of intermittent edema of her hands and feet. Examination revealed 3 plus albuminuria, hypoproteinemia and normal renal function (chart 1). An intravenous pyelogram was normal (fig. 1). At that time she had pyuria which was thought to be a lower tract urinary infection which responded promptly to streptomycin and has not recurred. Reference to chart 1 shows that all elements of function were studied and that this segmental analysis of the func-

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TABLE I

DATE	C_{PAH} cc/min.	E.B.F. cc/min.	C_{IN} cc/min.	TM_{PAH} mgm/min.	TM_G mgm/min.	B. P.	T. P.	Alb.	Glob.	Hematocrit
9-20-48			201		343	120/72	4.78	2.68	2.1	
10-18-48	791		116 112	72						
1-29-49	748	1245	114				4.5			40
5-15-51	333	920	114	73.5		125/85	4.8	3.0	1.8	42
5-16-51	5.16 Gms. proteinuria in 24 hours.									

C_{PAH} = para amino hippurate clearance. EBF = Effective renal blood flow.
C_{IN} = Inulin clearance. TM_{PAH} = Tubular mass for PAH
TM_G = Tubular mass for Glucose. B.P. = Blood pressure
T.P. = Total protein.

tional nephron was normal with the exception of the glomerular membrane. Albuminuria and lowered total plasma proteins indicate abnormal permeability. The low 15 and 60 minute PSP excretion in the presence of normal TM_{PAH} and TM_G indicates the fallibility of the PSP test rather than abnormal tubular function. Details of this graphic presentation of segmental renal function have been presented elsewhere.[5]

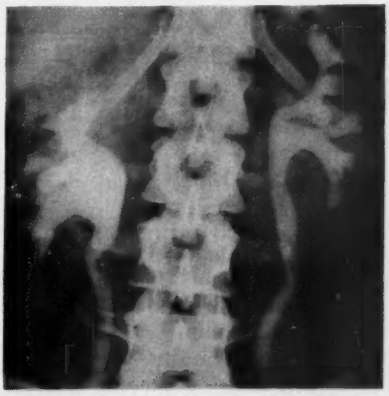
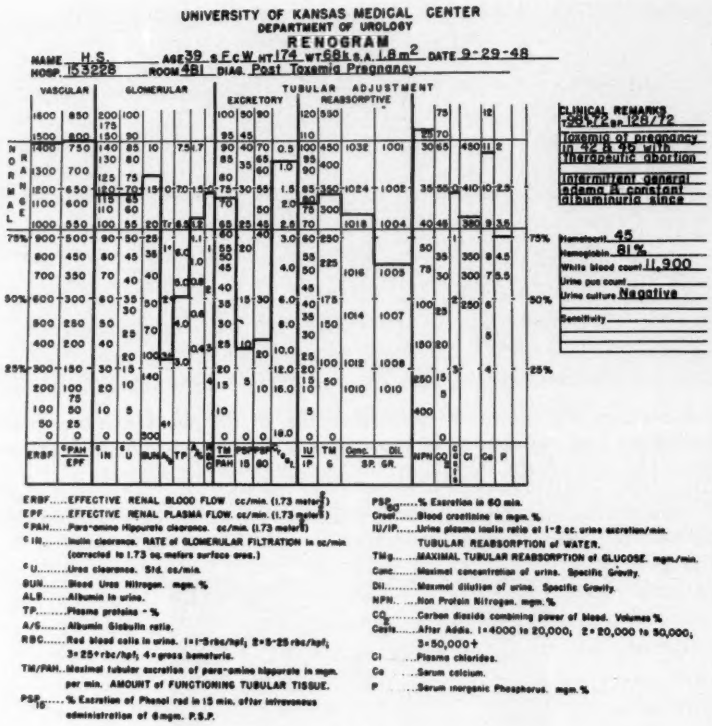


Fig. 1. Excretory pyelogram with compression bag on lower abdomen giving appearance of dilatation.

Her initial management consisted of a low protein intake, 0.5 Gm. for each Kg. of body weight, after the recommendations of Persike and Addis[6,7] but this was later changed to a diet of 2.5 Gm. of protein for each Kg. of body weight. On this regime she has maintained a low but stable plasma protein level and has had no clinically evident edema.

She has persistently exhibited 2 plus to 3 plus albuminuria. Her urine has been examined after periods of recumbency and found to contain an amount of albumin equal to that present during activity. Liver function tests are normal. Her renal function during the 32 month period of observation has not decreased and she has remained symptomatically well (table 1).



ERBF.....EFFECTIVE RENAL BLOOD FLOW cc/min. (1.73 meters²)
EPF.....EFFECTIVE RENAL PLASMA FLOW. cc/min. (1.73 meters²)
C_{PAH}.....Para-amino Hippurate clearance. cc/min. (1.73 meters²)
C_{IN}.....Inulin clearance. RATE of GLOMERULAR FILTRATION in cc/min (corrected to 1.73 sq. meters surface area.)
C_U.....Urea clearance. Std. cc/min.
BUN.....Blood Urea Nitrogen. mgm. %
ALB.....Albumin in urine.
TP.....Plasma proteins - %
A/G.....Albumin Globulin ratio.
RBC.....Red blood cells in urine. 1=1-5rbc/hpf; 2=5-25 rbc/hpf; 3=25+rbc/hpf; 4=gross hematuria.
TM/PAH..Maximal tubular excretion of para-amino hippurate in mgm. per min. AMOUNT of FUNCTIONING TUBULAR TISSUE.
PSP_{15}.....% Excretion of Phenol red in 15 min. after intravenous administration of 6 mgm. P.S.P.
PSP_{60}.....% Excretion in 60 min.
Creat.....Blood creatinine in mgm. %
IU/IP.....Urine plasma inulin ratio at 1-2 cc. urine excretion/min.
TUBULAR REABSORPTION of WATER.
TM/g.....MAXIMAL TUBULAR REABSORPTION of GLUCOSE. mgm./min.
Conc.....Maximal concentration of urine. Specific Gravity.
Dil.....Maximal dilution of urine. Specific Gravity.
NPN.....Non Protein Nitrogen. mgm. %
CO_2.....Carbon dioxide combining power of blood. Volumes %
Casts.....After Addis. 1=4000 to 20,000; 2=20,000 to 50,000; 3=50,000+
Cl.....Plasma chlorides.
Ca.....Serum calcium.
P.....Serum inorganic Phosphorus. mgm. %

Chart 1

Discussion

Persistent albuminuria in the absence of other signs of renal disease can be explained in two ways: either an abnormal albumin molecule somewhat smaller than the usual molecular weight of 70,000 is present, or an abnormally permeable glomerular membrane exists. The former possibility is attractive because the glomerulus will allow passage of substances with molecular weights only slightly under 70,000. However, in the presence of normal liver function (serum bilirubin, cephalin cholesterol, thymol turbidity, and icteric index) the likelihood of an abnormal albumin molecule is remote. On the other hand, most authorities agree that the fundamental lesion in preeclampsia is vascular[4,8,9] and that the typical renal lesion presents thickening of the basement membranes of the capillary vessels, resulting in ischemia of the glomerular loops. Dieckmann and Brown[10] disagree with this concept and feel that true preeclampsia causes no permanent vascular or renal damage. Decreased renal function is not a cause of preeclampsia and,

paradoxically, residual damage is more common after mild eclampsia than after the severe form.

One might question the diagnosis of preeclampsia during this patient's second pregnancy because it occurred before the last trimester. However, the history is typical; the patient was not certain exactly how long she had been pregnant, and authentic cases of preeclampsia have been reported as early as the fifth month.

It is worthy of note that the physical passage of large quantities of protein through the renal tubules does not in itself cause functional damage.

Conclusion

This patient had two episodes of preeclampsia causing sufficient damage to her glomerular membrane to allow passage and loss of large quantities of albumin but without functional renal damage and without hypertension.

A high protein diet in this case has caused no deleterious renal effects. This does not conflict with the concept of Persike and Addis because their recommendation of a low protein intake concerned patients with renal damage.

Summary

A case of persistent albuminuria for nine years following the first of two episodes of preeclampsia but without functional renal or liver disease or hypertension is presented after a 32 month period of observation.

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LIGATION OF SUPERIOR MESENTERIC VEIN*

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IT LONG has been believed that ligation of the portal or superior mesenteric vein would result in death. Although it has been repeatedly proved experimentally that complete and sudden ligation of the portal vein will cause death, graduated ligation is compatible with life.[1,2,3] There is now considerable evidence in case reports and experimental studies that the portal and superior mesenteric veins may be ligated in the human and in certain animals with very little evidence of immediate or late damage to the blood supply of the intestine.

CLINICAL CASE REPORTS

Recently Child et al.[4] have reported complete and sudden ligation of the portal vein in 2 human cases without any serious results.

The earliest case of mesenteric vein ligation we have found was that of Robson[5] in 1897. His patient received a penetrating wound of the abdomen with the sharp end of a file which severed the superior mesenteric vein. The divided vein was ligated with catgut. After the initial shock, the patient recovered without complication.

In 1901 Wilms[6] described a case of an 18 year old man who was wounded in the abdomen with a chisel. The tool passed through the left lobe of the liver and tore the superior mesenteric vein above the vena pancreatico-duodenalis. Some difficulty was experienced in controlling the bleeding from this and adjacent small veins. Ligation was not attempted. Thirteen hemostats were applied and left in situ for three days. The patient recovered.

The superior mesenteric vein was ligated by Colp[7] in a 27 year old man for pylephlebitis. This patient lived more than eight weeks and died with multiple liver and abdominal abscesses.

Brunschwig[8] was forced to ligate both portal and superior mesenteric veins in a case of carcinoma of the pancreas which involved these veins. The patient survived for 10 days and died of bile peritonitis.

Schnug[9] ligated a completely severed superior mesenteric vein in a man, aged 38, who had received a bullet wound in his abdomen. The bullet passed through the stomach and severed the superior mesenteric vein. This patient was heparinized for five days and given sulfadiazine for nine days. There was no evidence of internal or external bleeding after the operation. The patient recovered.

Parsons[10] reported a case of ligation of the superior mesenteric vein which had been invaded by cancer of the pancreas. His patient made a good recovery from the operation and lived five months.

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The following case report adds to the evidence that the superior mesenteric vein may be severed and ligated without any immediate or remote bad results.

L. R. C., a male, aged 52 years, was admitted to the University of Kansas Medical Center on Oct. 6, 1950, with a draining abdominal sinus at the site of an operation for carcinoma of the head of the pancreas which had been performed in February, 1950. At operation a sinus tract was found leading to the head of the pancreas. A cholecystoduodenostomy had been done. After exploration, the mass in the head of the pancreas was found to be movable and there was no evidence of metastases. The mass with the pyloric end of the stomach and duodenum was excised. The tumor involved the superior mesenteric vein and when an attempt was made to separate it from the vein, the vein was torn. Since the tumor had invaded the vein wall a section of the vein approximately 2 cm. long was removed with the tumor, and the vein was ligated. Ligation of the vein was done with the knowledge that Parsons had reported a similar experience without disastrous results. The fourth portion of the duodenum was closed. The severed end of the pancreas was closed with silk sutures. The antrum of the stomach and common bile duct were anastomosed to a loop of jejunum. A biliary fistula developed which persisted for a few weeks and finally closed spontaneously.

When the superior mesenteric vein was ligated the bowel and mesentery immediately became deeply cyanotic. The recovery of the patient was uneventful. There was no abdominal distention, diarrhea or evidence of bleeding from the intestinal tract. The highest postoperative temperature was 99.4 F.

The patient was dismissed from the hospital on the nineteenth postoperative day. He died on Aug. 24, 1951, 11 months after operation. An autopsy was not obtained.

Experimental Ligation of the Superior Mesenteric Vein

Experimental division and ligation of the superior mesenteric vein in dogs has resulted in a very high percentage of deaths in a few hours. Scott and Wangensteen[11] ligated this vein in one dog which resulted in death in one hour. These authors[12] concluded that animals with ligated superior mesenteric veins die of blood loss into the bowel and peritoneal cavity. Derr and Noer,[13] in a study of the revascularizing ability of the intestines of dogs, ligated and divided a branch of the superior mesenteric vein and arcuate veins, involving 15 cm. of the ileum or jejunum. In one series of 22 animals, 19 lived 10 days or longer.

Laufmann[14] observed that dogs with superior mesenteric vein ligation for two to four hours will live if given quantities of blood. The blood volume was ordinarily reduced 50 to 60 per cent. Heparin had no effect on such animals. In fact, Laufmann thought it possible that heparin actually hastened death by prolonging the coagulation time and thus permitting the animal to bleed more freely. He concluded that it is unsafe to administer heparin after operation in cases with impaired circulation of the intestine when the involved bowel is not resected.

Nelson and Kremen[15] produced death within four hours due to irreversible shock in all of their dogs in which the superior mesenteric vein was ligated. When given heparin, 6 of 8 animals survived. These authors state that heparin prevents intravascular clotting.

Schnug[16] ligated the superior mesenteric vein in dicumarolized dogs and states that he had some difficulty with hemorrhage. Some of his dogs survived. He was convinced that the superior mesenteric vein may be successfully ligated if anticoagulant therapy is used to prevent thrombosis from occurring in the collateral venous channels, thus allowing the development of collateral return.

In a somewhat different type of experiment Sarnoff and Poth[17] ligated the mesenteric veins of dogs halfway between the bowel and the root of the mesentery involving a segment of bowel 50 cm. long. No animal survived more than 45 hours. But when such animals were treated with succinylsulfathiazole for 10 days before ligating the veins, 70 per cent lived indefinitely. Because of the high mortality caused by portal vein ligation in the ordinary laboratory animals, Child and his associates used the macaca mulatta monkey. They ligated the portal vein suddenly and completely in 25 of these animals and 19 survived.

Summary of Our Experiments

In 19 dogs the superior mesenteric vein was ligated or sectioned and ligated (table 1). Sixteen of the animals lived an average of 11.5 hours. One animal lived 14 days. Two made a complete recovery and were sacrificed on the thirty-sixth and fortieth days after operation.

There is no evidence that heparinization before or after operation influenced the length of life. Dogs given sulfasuxadine before vein ligation lived an average of 26 hours. When streptomycin was given three days before vein ligation the average length of life in three animals was 4.6 plus days.

It is interesting to note that the only 2 animals that recovered did not have any treatment before or after section and ligation of the vein. Although the number of animals used is very small, the results indicate that the length of life of dogs with section and ligation of the superior mesenteric vein has not been significantly influenced by treatment with streptomycin, sulfasuxadine or heparin.

Discussion

No doubt there have been cases of superior mesenteric vein ligation resulting in death that have not been recorded. Pack[18] states:

TABLE 1

Results of Superior Mesenteric Vein Section and Ligation in Dogs

Dog	*Procedure*	*Length of Life After Operation*	*Gross Findings*
1	Simple Ligation	Died 8 Hrs.	Cyanotic gut, venous distension, blood-filled gut
2	Section and Ligation of vein	Sacrificed 36 days	Bowel appeared normal, moderate venous distension
3	" "	Sacrificed 40 days	Bowel appeared normal, prominent right spermatic veins but no definite anastomosis with mesenteric vein seen
4	" "	Died 7 Hrs.	Blood-filled bowel, marked venous distension and cyanosis
5	" "	Died 14 Hrs.	Cyanotic bowel, peritoneal bloody effusion, bowel contracted
6	Heparinized Section and Ligation of vein	Died 2 Hrs.	Cyanotic bowel, blood in gut and peritoneum
7	" "	Died 7 Hrs.	Cyanotic bowel, venous distension, blood-filled bowel
8	" "	Died 1 Hr.	Cyanotic bowel, venous distension, subserosal hemorrhage
9	" "	Died 4 Hrs.	Cyanotic bowel, venous distension, bowel filled with blood
10	8 Gm. sulfasuxadine 4 days, then section and ligation of vein	Died 8 Hrs.	Cyanotic bowel, venous distension, bowel spastic, no blood in lumen
11	" "	Died 47 Hrs.	Cyanotic bowel, venous distension, bowel filled with blood, bloody peritoneal fluid
12	" "	Died 18 Hrs.	Cyanotic bowel, venous distension, subserosal and intraluminal hemorrhage
13	" "	Died 13 Hrs.	Venous distension, blood filled bowel
14	1 Gm. per day streptomycin for 3 days, then section and ligation of vein	Died 24 Hrs.	Venous distension, cyanotic bowel, clotted blood in peritoneal cavity, bowel filled with blood
15	" "	Died 17 Hrs.	Venous distension, cyanotic blood-filled bowel
16	" "	Died 14 days	Venous distension, cyanotic blood-filled bowel
17	1 Gm. streptomycin for 3 days, Heparinization then section and ligation of vein	Died 3 Hrs.	Venous distension, cyanotic blood-filled bowel
18	" "	Died 2 Hrs.	Venous distension, cyanotic blood-filled bowel, subserosal hemorrhage
19	" "	Died 9 Hrs.	Venous distension, cyanotic blood-filled bowel, peritoneal bloody fluid

"Although ligation of this vein in dogs has been tolerated, in humans it has been followed in our bitter experience by mesenteric thrombosis, intestinal gangrene and death." He ligated the vein while resecting a carcinoma of the pancreas. One should, therefore, be cautious in drawing a definite conclusion that this vein may be ligated without fear of death. When the superior mesenteric vein is torn or severed in an accident or at the operating table, and anastomosis appears to be impractical or impossible, it is comforting to know that it may be ligated with the knowledge that the patient may have a chance to recover. It would be unthinkable that the section of the bowel drained by the superior mesenteric vein be resected since it extends from the mid-duodenum to the mid-colon (fig. 1).

It is well known that slow and gradual ligation of the superior mesenteric vein will not usually cause death and, therefore, it is reasonable to conclude that cases of thrombosis may have recovered when it was impossible to make an accurate clinical diagnosis.

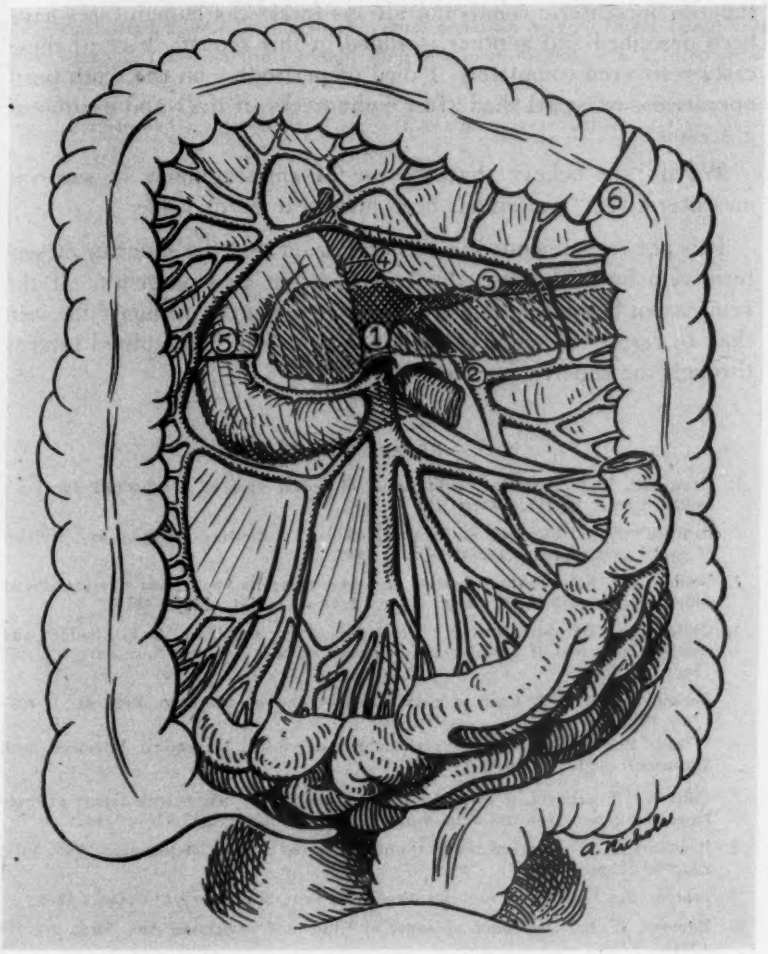
We would not have anyone believe that we consider ligation of the superior mesenteric vein a safe procedure. Whereas it was formerly always considered fatal, we now know that there are authenticated cases of recovery. In his report of ligation of the portal vein, Child conservatively remarked: "The most that can be said is that these 2 patients survived deliberate occlusion of their portal veins without any immediate untoward sequelae which could be detected clinically." The same may be said of the experience to date with superior mesenteric vein ligation.

It is apparent that dogs will not tolerate sudden ligation of the portal or superior mesenteric vein in a very high percentage of cases.

We have no idea what percentage of patients might die following complete and sudden ligation of the superior mesenteric vein. There have not been found any specific reports in the literature. The reference of Pack suggests that ligation may be fatal in some cases.

Since ligation of the superior mesenteric vein will very probably always be an emergency operation, the knowledge that preoperative therapy may be of value, as indicated in certain reported experiments, is not very helpful in the treatment of emergencies.

Anastomosis of a severed mesenteric vein should be attempted in selected cases. After removal of a 3 cm. section of a mesenteric vein with a carcinoma of the pancreas, Moore, Sako and Thomas[19] were able to make an end to end anastomosis of the vein with recov-



This illustration represents the anatomy usually found in textbooks. The inferior mesenteric vein may enter the superior mesenteric vein instead of the splenic. Purcel et al. [Arch. Surg. (May) 1951] found the inferior mesenteric vein entering the superior mesenteric vein in 53 per cent of 100 dissections.

ery of their patient. These authors believe that their case is the only one of its type recorded in surgical literature.

Conclusions

A positive statement cannot be made that ligation of the superior mesenteric vein is without danger to life.

The clinical cases here collected are proof that ligation of the

superior mesenteric vein is not always fatal. Six human cases have been described and another is added in this report. Five of these cases recovered completely, 1 died of peritonitis on the tenth postoperative day, and 1 died after eight weeks of liver and peritoneal abscesses.

We do not believe that the use of anticoagulants in superior mesenteric vein ligation has been proved to be of value.

It is not recommended in this discussion that the superior mesenteric vein be deliberately ligated except in an emergency. If the vein cannot be repaired or anastomosed it is safer to ligate the vein than to resect the segment of bowel from which the blood returns through the superior mesenteric vein.

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METHODS OF REPAIRING EXSTROPHY OF BLADDER

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EXSTROPHY of the bladder is a congenital defect occurring about once in 40,000 to 50,000 births.[1] Arrested development of the anterior allantois and abdominal wall leaves the posterior aspect of the bladder exposed.[2] This condition is variously reported to occur in a ratio of 5 males to 1 female. About half of these patients die in infancy from an ascending urinary infection due to constant exposure and irritation of the bladder.

Occasionally a few patients live to be 20 years of age if untreated. There is a surprisingly low incidence of carcinoma of exstrophic bladders in view of the constant irritation.[3] The degree of bladder exposure varies from a narrow cleft to a wide separation. Definitive therapy in all instances should accomplish colonic diversion of the urine and removal of the exstrophic bladder. Attempts to close the bladder defect, beginning in 1852 by Roux, have been uniformly unsuccessful. The problem of urinary diversion with its attendant surgical and physiologic problems will not be considered in this paper.

After cystectomy the surgical defect must be adequately covered. Adjacent unscarred tissue must be transplanted as a flap without tension to fill the defect. Absence of the bony symphysis and lower abdominal muscles make adequate coverage of the cystectomy defect imperative. These deficiencies vitiate any attempt to close such defect without additional tissue. A properly planned and fashioned flap provides coverage, protection from trauma, and simplifies later genital reconstruction. In the female a flap may be raised from the adjacent inguinal area. The patterned flap should be raised with uniform thickness. The skin and subcutaneous tissue are incised down to the abdominal fascia. The base of the flap should contain the superficial epigastric artery and vein to insure viability. Such a flap has the advantage of immediate transfer and quick healing.[4]

If circulation to the mobilized flap appears adequate, it can be rotated into the cystectomy defect. The transfer must be deferred if the rotated flap is pale or cyanotic, or if the edges do not bleed freely. When a flap shows any sign of circulatory insufficiency, it must be returned to its original site and transplantation delayed. Usually rotation of a delayed flap can safely be carried out in from 10 to 14 days.

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In general a flap should border the defect, be placed in an area free of scar, and be one-third to one-fourth larger than the cystectomy defect to allow for shrinkage. Catgut sutures should approximate the subcutaneous tissue of the flap to the periphery of the cystectomy defect. Interrupted silk sutures placed without tension complete the closure of the contiguous skin surfaces. The transplanted flap should have a normal color and blanch on pressure. The donor bed of the flap is then covered with a split thickness skin graft. Pressure dressings are applied to the flap and skin grafted areas. Healing is usually complete in 7 to 10 days. Reconstruction of the vulva should be deferred in children. When the patient passes the age of puberty, the cleft anterior labial commissure can be closed and a functional vagina constructed.

CASE 1. D. S. B. At the age of 3 months, on Oct. 26, 1950, this white female had bilateral ureterosigmoidostomies performed. She had hyperchloremic acidosis for two months postoperatively and was well thereafter. On July 26, 1951, at the age of 12 months, cystectomy and flap coverage were performed (figs. 1, 2). The figures show the pre- and postoperative condition. Adequate healthy tissue is present for primary coverage and for ultimate reconstructive purposes.

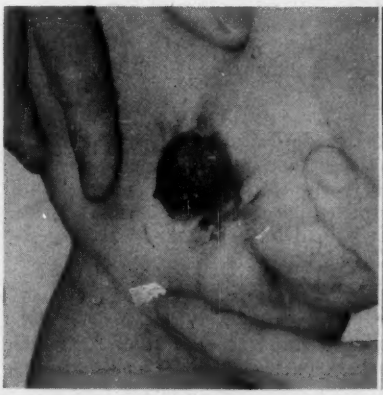

Fig. 1. Bilateral ureterosigmoidostomies have been performed for diversion of urine at the age of 3 months.

Fig. 2. An adjacent flap has been rotated into the bladder defect. One stage coverage with normal tissue providing protection and aiding later genital reconstruction.

CASE 2. N. C. At the age of 4 years this white female had right and left ureterosigmoidostomies performed on March 19, 1949, and on April 19. In May, 1949, cystectomy was performed, leaving a 4 by 8 cm. defect to cover. By undermining skin edges and direct suture, an attempt to close this defect failed. Due to tension the repair broke down and healed by cicatrix (fig. 3). In July, 1949, the scarred cystectomy defect was excised and immediate rotation flap coverage obtained (fig. 4).

In males with exstrophy and epispadias the coverage problem differs only in its genital aspects. In addition to coverage of the cystectomy defect, an attempt should be made to connect the reconstructed urethra to the prostate. Correction of this combination of anomalies calls for an indirect transplantation of tissue from a distance.

Fig. 3. Colonic diversion of urine done at the age of 4 years. One month later cystectomy was performed. Attempted closure of defect by undermining and direct suture failed because of tension.

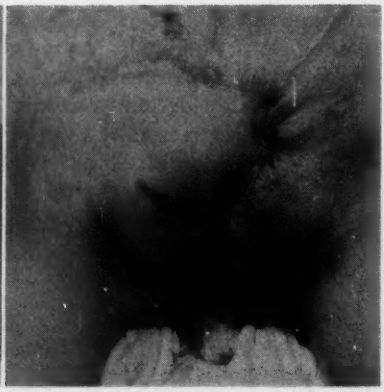

Fig. 4. Two months after unsuccessful closure the scarred cystectomy defect was excised. A rotated flap was elevated and transplanted without tension to fill the defect. Split thickness skin graft applied to cover donor area of flap.

A Gillies tubed pedicle flap[5,6] should be patterned with its long axis in line with the vascular supply of the adjacent donor bed. Since a tubed flap will shrink in both length and width, it is wise to raise a flap about one-third larger than the defect. In general a bipedicle tube should have a ratio of width to length of not more than 3 to 8.[7] It is inadvisable to extend a tubed flap across the midline of the body because of blood supply.

A tubed pedicle flap is fashioned by making two parallel incisions through the skin down to the abdominal fascia. The defect may be closed by direct suture. If this is impossible, a split thickness skin graft may be used. Tubing a flap has the advantage of closing a raw surface with a minimum of scar formation and shrinkage. After about three weeks the bipedicle tube should have an adequate blood supply. One or two proximal serial delays done under local anesthesia will demonstrate whether circulation is adequate for transfer.

The urethral channel can then be closed by means of local flaps[8] and the bladder excised. The proximal delayed end of the tube is then rotated to provide external coverage for the urethra and cystectomy defect. The tube is opened along the seam, unfolded and the desired amount of tissue is present for coverage. The distal end of the tube based in the inguinal area should be left attached for blood supply. Severance and revision of this distal pedicle can be done safely in from three to four weeks.

Case 3. E. H. This 30 year old male with exstrophy and epispadias underwent a series of operations in 1941 by Dr. E. C. Padgett, who fashioned a tube

as described above to cover the bladder and urethra for urinary drainage. For a short time this closure was successful and incontinent urinary drainage was obtained from the penis. Multiple urinary fistulas soon developed at the periphery of the bladder causing him to resume the life of a social outcast. In June 1950 he again sought help and on June 6 bilateral ureterosigmoidostomies were performed. On August 15 cystectomy was performed and the tube overlying the bladder was opened and sutured into the operative defect. Since the tube had been attached at both ends for several years, the redundant portion of the tube was removed at the time of closure (fig. 5).

Fig. 5. Transferred pedicle tube provides coverage for the dorsum of the penis and cystectomy defect.

This patient has a functional urethra and reports ejaculation to occur. He is gainfully employed for the first time in his life and seeks normal social relationships.

SUMMARY

The genital problems of exstrophy of the bladder in male and female are discussed and methods of repair presented.

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A NEW INSTRUMENT FOR VAGINOSCOPY AND ANOSCOPY

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DURING examination of the vagina or the anus it may sometimes be difficult to obtain the right illumination, especially if the examination takes place in the patient's home or in the doctor's office. For this reason the author has modified the commonly used blades for vaginoscopy and anoscopy to fit into a handle containing a dry cell battery and carrying a small electric bulb (figs. 1, 2). Electrical contact is made by turning the end cover. The only insulated part is a short metal bar which makes the contact between the bulb and the dry cell battery; it thus contains no electric wires or cords to get out of order.

Fig. 1. The vaginal speculum attached to the Morch handle.

Fig. 2. An anoscope attached to the Morch handle.

The blades are easy to change as they slide in and can be pulled out like a drawer between two small grooves on the handle (fig. 3). The instrument is made in Denmark and also in the United States. In the Danish instrument the blades are held in place by means of a small milled fingerscrew; in the American design by means of a small spring.

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The blades carry no electric bulb or wire and may be sterilized by boiling or autoclaving.

The anoscope blade is available in two sizes. The blades are relatively simple in construction so it would be inexpensive to have additional blades made according to the need and ideas of the individual doctor. To illustrate this it may be mentioned that the author has had blades made for several different purposes; *e.g.* for oral surgery (cheek retractors, tissue retractors, straight and angled

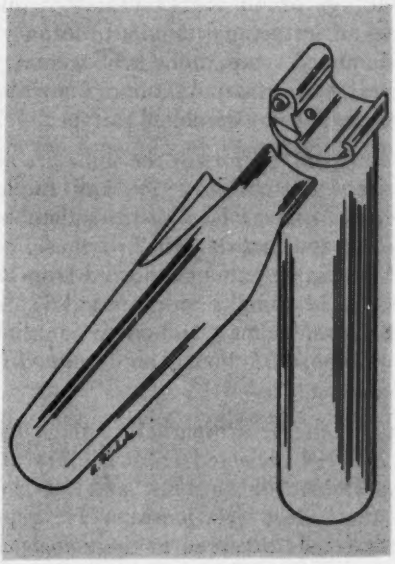

Fig. 3. The blades slide into two grooves in the handle.

tongue depressors) and several blades for laryngoscopy (straight and curved blades in different sizes for all sizes of patients from the premature to the largest adult).

The instrument was developed in 1948 through the encouragement and advice of my old friend, Major Ole Lund Lippmann, M.B.E., and Richard Foregger, Ph.D. It is available through the firms Simonsen & Weel of Copenhagen, Denmark, and The Foregger Co., New York, N. Y.

DUMBBELL TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM

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INTRASPINAL tumors are uncommon in childhood. Of 451 spinal cord tumors reported from the Mayo Clinic by Adson,[1] only one occurred under the age of 10 years. Hamby[2] collected from the literature 100 cases of intraspinal tumors in infancy and childhood, 4 of which were dumbbell sympathetic neurogenous tumors. Ingraham[3] reported 16 cases of intraspinal tumors in children, 1 of which was a neuroblastoma, but not dumbbell in type.

Dumbbell, or hourglass, tumors of the spine are not rare. Heuer[4] reviewed the entire literature in 1929, and found 64 cases, the majority being neurofibromas. Five of these dumbbell tumors were classified as ganglioneuromas, though 2 of these, case 16 and case 28, are apparently the same patient reported from different sources. Eden,[5] in a series of 234 spinal tumors, found 32 dumbbell tumors, 25 of which were neurofibromas, and one a ganglioneuroma. Naffziger and Brown[6] report 15 hourglass tumors of the spine, one being a ganglioneuroma.

Tumors arising from the sympathetic anlage have long excited interest. Wahl[7] in 1914 collected from the literature 47 cases of ganglioneuromas, 25 neuroblastomas, and 12 chromaffin tumors and emphasized their close relationship. He reported 1 case in which all 3 types of cells occurred in the same neoplasm. Willis[8] points out that all tumors of the sympathetic anlage should be considered as a group, merely representing various grades of malignancy. The ganglioneuromas usually arise from the sympathetic chain and are considered benign, and the neuroblastomas usually arise from the adrenal medulla, metastasizing widely. Both tumors are common in childhood.

The syndrome of dumbbell neurogenous tumor is apparently quite rare. In 1950, Sames[9] reviewed the literature, finding 7 reported cases and added 1 of his own. Loretz[10] described the first case of ganglioneuroma in 1870, discovered at autopsy in a female of 35. Although this tumor surrounded the transverse process of the second thoracic vertebra, no mention is made of its invading

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the intervertebral foramina. In 1915, Anitschkow[11] reported the case of a 4 year old child who died following laparotomy for an abdominal mass. Autopsy revealed a dumbbell ganglioneuroma presenting intraspinally and extradurally from the third to the fifth lumbar vertebrae and extending through the fifth vertebra to become a large intra-abdominal mass. This case was not included in Sames's review of the literature.

Rapp[12] reported in the same year 36 cases of sympathetic nervous system tumors, one of which was a dumbbell ganglioneuroma. This occurred in a 4 year old male with progressing paraplegia and a large abdominal tumor. The tumor was adherent to the right side of the spinal column and extended from the tenth intercostal space to the iliac crests. It enclosed two transverse processes and extended extradurally within the spinal canal, compressing the dura.

Stout[13] reported in 1924 the case of a 2½ year old male with a mediastinal tumor and paraplegia. This is the same case reported also by Elsberg.[14] A needle biopsy specimen of the chest tumor revealed neoplasm containing ganglion cells. Laminectomy by Elsberg seven months later revealed an extradural intraspinal neoplasm continuing into the chest through the upper right thoracic intervertebral foramina. Total intraspinal removal was accomplished, but the child died postoperatively. Microscopic examination of this neoplasm revealed ganglion cells similar to those seen in the biopsy specimen of the chest tumor.

In 1927, Cushing and Wolbach[15] reported the unusual case of a male child 1 year and 9 months old who was paraplegic and had a paravertebral swelling. Biopsy specimen of this mass was reported as spindle-celled sarcoma. Clinical improvement of all but the paraplegia followed the use of Coley's toxins. Ten years later, laminectomy by Cushing revealed an intraspinal extradural ganglioneuroma which was successfully removed. The original tissue from the paravertebral mass was reviewed and the diagnosis of neuroblastoma was made. The authors felt that in this case an original malignant dumbbell neuroblastoma had matured into a benign ganglioneuroma.

In 1927, Capaldi[16] reported a 2 year old female who died following the removal of tissue for biopsy of a large irregular tumor about both clavicles. Autopsy revealed a large intrathoracic tumor which had broken through the intervertebral foramina from the seventh to twelfth thoracic to present as an intraspinal extradural mass. His histologic diagnosis was neuroblastoma, though his reproduced photomicrograph shows mature ganglion cells. Sames did not include this case in his review of dumbbell ganglioneuromas.

In 1933, Naffziger and Brown[6] reported the case of a 7 year old male with paraplegia and roentgenologic evidence of a mass in the right chest. Laminectomy revealed an intraspinal extradural tumor which was removed. The child died three months later of a huge tumor filling the right chest. The final pathologic diagnosis was ganglioneuroma.

In 1941, Eden[5] reported the case of a 23 year old male who, at the age of 5 years, had been seen with partial paralysis of the legs, and roentgenograms had revealed a mass in the chest. No therapy was given, and the patient spontaneously recovered. Eighteen years later the paraplegia recurred, and roentgenograms again revealed a large tumor mass in the left chest. Death followed thoracotomy, and autopsy revealed the chest tumor passing through several intervertebral foramina to become an intraspinal extradural neoplasm compressing the dura. Microscopically, the tumor was considered a ganglioneuroma. The long remission in this case is strikingly similar to the case reported by Cushing and Wolbach, and again suggests the possibility of a malignant neuroblastoma maturing into a benign ganglioneuroma.

In 1941, Paterson and Pilcher[17] reported a 4 year old male with a mass in the chest and no neurologic evidence of intraspinal involvement. Spinal puncture was not done. By thoracotomy, total removal of the tumor was accomplished, though at operation a projection of the tumor was found extending into the fourth intervertebral foramen. Microscopically the tumor was a ganglioneuroma.

In 1950, Sames[9] reported a 3 year old paraplegic female with a calcified tumor mass revealed by roentgenogram in the right posterior mediastinum. Laminectomy revealed an encapsulated intraspinal extradural tumor compressing the dura and passing through the right fifth intervertebral foramen. The chest tumor was removed three months later by mediastinotomy. The pathologic diagnosis was ganglioneuroma. The paraplegia cleared up, and there was no clinical evidence of recurrence in five years. This is the first example of successful removal of an intraspinal ganglioneuroma by laminectomy followed by removal of the chest tumor by thoracotomy.

Case Reports

Case 1. D. L., a 3 year old white female, was admitted to the University of Kansas Medical Center, Jan. 31, 1951. The parents had noted progressive disturbance in the child's gait for one month, and the child had complained of numbness of the legs for one week.

On examination, the child was barely able to walk because of a spastic paraparesis, with hyperactive deep tendon reflexes in the lower extremities,

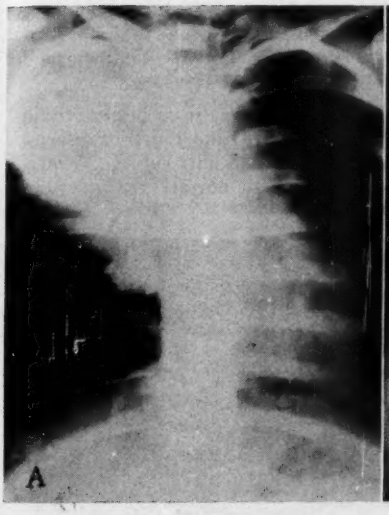

Fig 1a. Roentgenogram of chest of case 1.

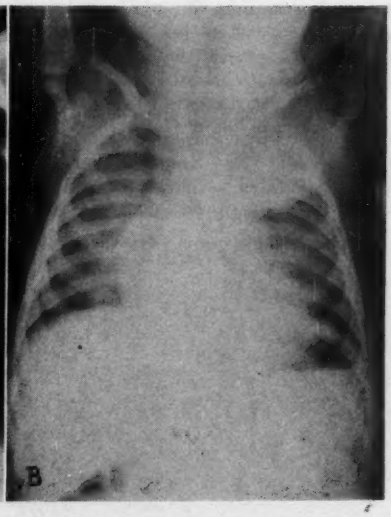

Fig. 1b. Roentgenogram of chest of case 2.

Fig. 2. Operative photograph of intraspinal portion of tumor of case 1.
A. Tumor. B. Dura.

absent abdominals, bilateral ankle clonus, and bilateral positive Babinski's sign. There was no positive objective sensory impairment, and no abnormal neurologic signs in the upper extremities or cranial nerves. Dullness and decreased breath sounds were found over the right upper chest.

Roentgenograms of the chest (fig. 1a) revealed a large mass posteriorly in the upper right chest, with erosion of the second, third, and fourth transverse processes and ribs. Routine laboratory studies were noncontributory. A myelogram revealed a complete block opposite the fourth dorsal vertebra. The spinal fluid protein was 66.7 mg. per cent.

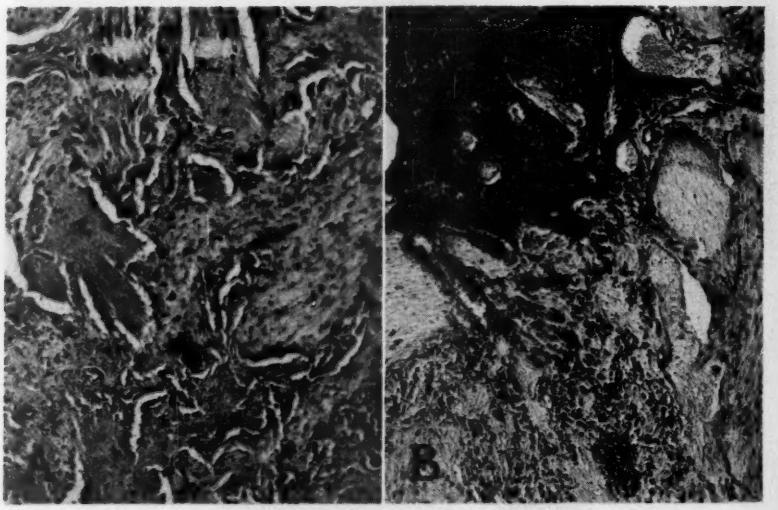

Fig. 3a. Photomicrograph, case 1, showing bundles of neural fibrils with scattered immature ganglion cells and occasional foci of calcification. Hematoxylin and eosin. X 70.

Fig. 3b. Photomicrograph, case 1, of metastasis in lymph node replacing greater part of lymphoid tissue. Immature ganglion cells are numerous. Hematoxylin and eosin. X 70.

Laminectomy of first through fifth thoracic vertebra was performed Feb. 6, 1951. An encapsulated intraspinal extradural tumor (fig. 2) was found on the right lateral aspect of the dura, markedly compressing it to the left. It extended into the chest through expanded second, third, and fourth right intervertebral foramina, ensheathing the three intercostal nerves. It was firm, purplish brown in color, and readily stripped from the dura. Total gross removal was easily accomplished, sacrificing the three involved intercostal nerves. Tumor was curetted from the intervertebral foramens, and this region thoroughly cauterized. On February 16, thoracotomy was performed by Dr. Paul Schafer and a tumor mass 12 by 5 cm. was removed. Invasion across the midline and up into the neck made total removal impossible. The postoperative recovery from each procedure was uneventful, and recovery of normal use of the legs was complete upon dismissal from the hospital on February 25.

The patient was readmitted to the hospital May 5, 1951, because of a palpable mass in the right supraclavicular fossa. Neurologic examination was negative but for a right Horner's syndrome which had not been present pre-

viously. This mass was approached surgically May 8, and proved to be a discrete nodule 3 cm. in diameter which shelled out easily and did not appear to be direct extension into the neck from the chest tumor as the surgeon (WPW) had anticipated. A nearby separate lymph node was also removed. The child was dismissed from the hospital May 13 and last seen July 18, at which time the only positive neurologic finding was a right Horner's syndrome. Chest roentgenograms were negative, and one small cervical lymph node was palpable.

The specimen from the spinal canal was an irregular, lobulated, rubbery mass, 7 by 2.5 by 1 cm. Part of the surface was smooth and encapsulated, presenting somewhat of a bosselated appearance. Attached to this mass was a flat ribbon of tumor branching to anastomosing, which formed a lattice pattern, the width of these being up to .6 cm., and thickness .1 to .2 cm. The opposite surface was irregular. Cut section revealed a yellowish-white glistening mass with foci of hemorrhage. All specimens were fixed in 4 per cent formalin, stained by Hematoxlyn and Eosin, Fuchsin-Methylene blue, Bodian's, Wilder's reticulum, Phosphotungstic Acid Hematoxylin and Cajal's reduced silver method.

Microscopic section revealed some areas of the tumor, especially near the periphery, to be composed of nerve bundles in a loose fibrous stroma. The greater part of the tumor was composed of less distinct bundles of neural and fibrous elements. In the latter part were areas generally devoid of stromal nuclei, but variable in size and shape, and having a feathery to fibrillar matrix (fig. 3a). Throughout the fibrous areas, and to a greater extent in the feathery areas, were scattered groups of ganglion cells in various stages of development. The smaller of the least mature cells were approximately 10 microns in diameter, and had sparse cystoplasm and nuclei less chromatic than lymphocytes. Some of the ganglion cells had axons; the nuclei of these had prominent nucleoli. Larger cells containing two to three nuclei were common. An occasional large ganglion cell showed vacuolization of the cytoplasm, degeneration, and were surrounded by satellite cells. Mitoses were not seen. Thin walled blood vessels occasionally showed paravascular foci of lymphocytes.

The second specimen removed from the chest was a flattened discoid mass, 12 by 5 cm., weighing 275 Gm., and in part having a bosselated to nodular surface. The larger nodules measured up to 1 cm. in diameter. Cut section of the tumor revealed a pale yellow color with intertwining white translucent fibrous bundles. It was rubbery in consistency, and contained foci of hemorrhage. A brown soft zone, 1.5 by .6 cm., was noted near the pleural surface.

Microscopic section revealed the pleural covering to be associated with a thin fibrous zone, under which there were interlacing bundles of nerve fibers. Ganglion cells were present in the larger bundles. This part of the tumor suggested sympathetic ganglia, except for the aimless pattern of the numerous nerve bundles. The architectural pattern otherwise was similar to that noted in the intraspinal mass, except that greater numbers of lymphocytic foci were seen. In some of these inflammatory foci, plasma cells and polymorphonuclear leukocytes were also present. The inflammatory foci were also paravascular, or near the periphery of the tumor in distribution, as was noted in the previous specimen.

The third specimen received some 11 weeks later consisted of two flattened spheroid masses, 4 by 4 by 1.8 cm. and 1.5. by .6 cm. Adherent tags of fat and fibrous tissue were attached to the smooth capsule. Cut section revealed the larger to have gray trabeculae in a yellowish-gray substance. A few

petechiae were noted. The nodes were rubbery in consistency. Microscopic examination revealed the greater part of the nodes to be replaced by tumor; however, the capsule, peripheral sinusoids, and some germinal follicles were still recognizable (fig. 3b). The tumor again presented the pattern of anastomosing bundles of nerve fibers, in which there were irregular nests of ganglion cells in varying stages of development.

Diagnosis: Ganglioneuroma, intraspinal and paravertebral with cervical lymph node metastases.

The tumor is of interest for two reasons: its dumbbell character, and the presence of metastases. Stout[18] divided ganglioneuromas into three groups according to stage of differentiation: (1) A fully differentiated one which does not metastasize; (2) a partly differentiated one which occasionally gives rise to metastasis (18.2 per cent); and (3) a third small but complex group made up of both fully differentiated ganglioneuroma nodules and fully malignant sympathicoblastomatous nodules, the great majority of which metastasize (65 per cent). Our tumor falls into the partially differentiated group. The metastatic lesions in our case were quite similar to the primary tumor. Six cases of Stout's group II metastasized, and in 2, Berner,[19] and Miller,[20] the metastases were less differentiated. Dunn's[21] case is reported to have had metastases resembling neuroblastoma. In Stout's[18] case 9, the tissue examined was a lymph node which contained a metastasis of a partially differentiated ganglioneuroma; the architecture of the original tumor was not known. In Lewis and Hart's[22] case, local recurrence and lung metastases are mentioned but no description was given. Capaldi's[16] case as mentioned above had extensions into the axilla and neck. The author states that what was thought to be metastases were not, but were continuation of the primary tumor by expansive growth.

It is of interest that both the tumor and metastases in our case are composed of predominantly well differentiated elements. We assume the less differentiated elements metastasized and later underwent differentiation. The presence of lymphocytes in these tumors has given rise to the hypothesis that they are undifferentiated neuroblasts, hence the source of metastases. We feel that the paravascular location and presence of occasional polymorphonuclear leukocytes and plasma cells in the groups of lymphocytes would seem to indicate that these foci are inflammatory.

CASE 2. J. C., a 5 month old male, was admitted to the University of Kansas Medical Center July 31, 1951. Four weeks previously, the parents noted clonus when they stood the child on his feet. For three weeks he had not eaten well and had acted tired, and for one week he would scream every time his feet were held up for his diapers to be changed. The referring pediatrician had noted abdominal type of breathing, ankle clonus, and hyperactive reflexes in the legs. Spinal puncture had been done which revealed xanthochromic fluid with a total protein of 600 mg. per cent. Chest roentgenograms had disclosed a mass in the left upper lung field.

The birth history was negative. The child had never sat up or crawled. He had gained weight until two weeks before admission, but had lost 14 ounces since then.

Examination revealed a healthy appearing child who lay quietly in bed, but became irritable when disturbed. His neck was stiff. There was dullness and decreased breath sounds in the left upper chest. There was moderate spastic weakness of both legs, with hyperactive deep tendon reflexes, clonus, and

Babinski's sign. The abdominal reflexes were absent, there was normal function of the arms, and sensation was apparently intact.

Roentgenograms of the chest (fig. 1b) revealed a mass posteriorly in the upper left chest with probable erosion of the second, third, and fourth ribs.

Fig. 4. Operative photograph of intrathoracic portion of tumor, case 2. A. Tumor. B. Aortic arch (lung retracted).

Laminectomy of the first through the fifth vertebrae was performed on Aug. 4, 1951, and an encapsulated intraspinal extradural tumor was found, grossly entirely similar to the tumor in case 1. It lay on the left side of the dura, markedly compressing it, and extended into the chest through enlarged first, second, and third left intervertebral foramina, completely ensheathing each of the intercostal nerves. Gross total intraspinal removal was accomplished, sacrificing the three intercostal nerves and curetting the tumor out of the involved intervertebral foramina. On August 18, thoracotomy was performed (fig. 4) by Dr. Paul Schafer, and the intrathoracic mass was removed, though invasion of surrounding tissues made total removal impossible. The postoperative course of both procedures was uneventful. The child was dismissed August 27 to receive deep roentgen therapy elsewhere. The spasticity, clonus, and Babinski's sign had disappeared, though a left Horner's syndrome, which had followed intraspinal surgery, persisted.

The specimen from the spinal canal was submitted in three pieces which, when reassembled, formed an elongated, irregular, ragged, slightly lobulated, dark-gray mass 3 by 1.5 by .5 cm. The tissue was soft and spongy. Fragments of adipose tissue on a whitish-gray fibrous membrane were on one surface.

The second specimen removed from the chest consisted of a larger, lobulated mass, 4 by 4 by 5 cm. which weighed 24 Gm. and was, in part, encapsulated. The opposite surface was irregular and had numerous fibrous tags and adipose tissue attached. Six smaller rounded fragments were 1 by .6 by .5 cm., and had a pink color with apparent gray follicles on cut section.

Section of the larger mass revealed a grating sensation with the knife. The surface was dark-gray, hemorrhagic, and a soft 2 cm. area of necrosis, with whitish-gray foci, was noted. The tumor elsewhere had a poorly outlined lobular pattern, and was soft and cellular in consistency. Near the area of attachment was noted a firmer, gray triangular zone.

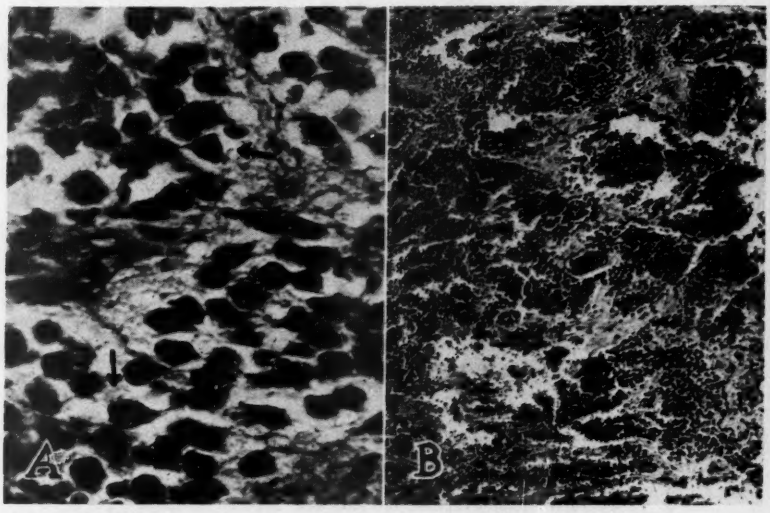

Fig. 5a. Fibrillary character of the ground substance and an occasional cytoplasmic process (arrows) seen in case 2. Bodian's stain. X 700.

Fig. 5b. Photomicrograph, case 2, showing incomplete separation into an alveolar pattern and clumping of the tumor cells. Bodian's stain. X 70.

Microscopic sections of the two specimens were quite similar, except for the greater amount of calcium present in the tumor tissue removed from the chest. The tumor had a capsule of varying thickness, with trabeculae extending into the tumor mass, dividing it into irregular sized compartments. Much of the tumor showed recent hemorrhage, degeneration and calcification. In the areas showing less degeneration, there was a tendency for the larger masses of tumor cells to be incompletely divided into smaller groups by more delicate fibrous strands bearing blood vessels (fig. 5b). The tumor cells tended to clump, but showed no tendency to form rosettes. These tumor cells were approximately one and one-half times the size of lymphocytes, with sparse acidophilic cytoplasm and chromatic nuclei. Small processes extended from some cells and fibrillary strands were seen in some less dense nests of tumor cells (fig. 5a). This fibrillary material did not stain as reticulum. However, Cajal's method stained an occasional process arising from the tumor cells. The nuclei had a distinct cell wall, the chromatin was clumped or reticulated, and a rare nucleolus and mitotic figures were seen. Some lymphocytes and polymorphonuclear leukocytes were seen in the supporting stroma, as well as in the areas of degeneration. The lymph node was replaced for the most part by tumor, in which some degeneration and foci of calcification were noted.

Diagnosis: Sympathicoblastoma, intraspinal and paravertebral with lymph node metastases.

SUMMARY

Two cases of dumbbell tumors of the sympathetic nervous system are reported, with a review of the literature of previously reported cases.

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THE APPLICATION OF A TRANSVERSE TRANSSTERNAL INCISION FOR THE SURGICAL EXPOSURE AND EXCISION OF LARGE ANTERIOR MEDIASTINAL TUMORS

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A 25 YEAR OLD white male presented a large anterior mediastinal tumor on roentgenologic examination. Because of the large size of the mediastinal opacity it was contemplated that a bilateral thoracic approach through the sternum might be necessary for the extirpation of the tumor if it was found to be removable on surgical exploration. At operation on Nov. 17, 1949, through an exploratory thoracotomy incision, the mass was thought to be free of vital mediastinal structures, but could not be completely dissected circumferentially nor extracted in toto. The second intercostal incision was then carried transversely across the body of the sternum to the opposite chest. The ensuing ease of dissection, the complete removal of the mass and the subsequent absence of impairment of respiratory function was an impressive demonstration of the possible indications and uses of such a surgical approach. The facility and relative safety of transverse sternal incisions have been attested to in succeeding patients with pathologic conditions of the superior mediastinum, some of which are reported here. Although Friedrich[1] adequately described such an incision in 1910, it has not been in popular use generally. Muller[2] recently called attention to a transsternal approach for exposure of the anterior mediastinum and for the surgical treatment of constrictive pericarditis.

The sternum is respected by surgeons because of the important role it plays in the function of respiratory movements. It serves as the anterior fixed bony attachment for the movable "pail-handle" ribs with the intercostal muscles, and, to a certain extent, for the diaphragm and cervical muscles of respiration. Absence of such bony fixation anteriorly results in altered and inefficient respiratory movements, often called "paradoxical respiration," which may, if unattended, result in fatal anoxia. In spite of this rather formidable limitation, surgeons have been dividing, splitting, reconstructing, and also excising the sternum or portions of it with reasonable success when precautions have been taken to provide the necessary fixation of the anterior bony cage of the thorax.

Large mediastinal tumors occasionally present two problems in

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relation to their successful surgical removal. One concerns the necessity for accessibility, or adequate exposure for dissection of the tumor through the operative field. The other concerns the extraction of the large mass of tissue without rupture or surgical division. Several incisions and surgical approaches are described for the removal of mediastinal tumors and are employed by surgeons today. For the most part these incisions are comparatively adequate for the usual small to moderate sized tumors, but lack one or both of the more desirable features mentioned above when one is dealing with large tumors. It is conceivable that removability of such tumors may be entirely dependent on the incision or approach.

Many mediastinal tumors situated in the anterior superior mediastinum are removed satisfactorily through a transverse cervical (collar) incision. If such tumors are too large for extraction through the rather rigid superior thoracic inlet (usually 5 cm. in anteriorposterior diameter), a sternal splitting (longitudinal) incision, such as described by Sauerbruch,[3] is sometimes employed. Large mediastinal tumors may not be removable through this incision. A mediastinotomy incision was described by Milton[4] in which the sternum is divided longitudinally from the episternal notch to the zyphoid process. The exposure employing Milton's incision is adequate but the approach has the disadvantages of blunt retrosternal dissection for a rather long area; repeated chances for entrance into either pleural space or peritoneal cavity; and disruption of costal breathing by removal of all the anterior fixation of the chest wall. Transperiosteal and intercostal (transthoracic) incisions, transpleural or extrapleural, are commonly employed for many mediastinal tumors, but often only one side or surface of a midline tumor may present itself for dissection. Modifications of the above, such as parasternal incisions and "trap-door" approaches, may still be limited when dealing with large anterior mediastinal tumors.

In Friedrich's description of the "transverse sternothoracotomy" the skin incision is placed at the level of the third ribs, the sternum is divided transversely and the second interchondral spaces are incised. Graham[5] utilized a transverse incision at a more inferior level of the sternum for the removal of a large adherent tumor in the lower anterior mediastinum.

To illustrate the facility of the transverse sternal surgical approach a small series of cases is briefly presented here in which large anterior mediastinal tumors could not have been exposed satisfactorily or removed in toto had a transverse transsternal incision not been employed for the surgical approach. The incision, although

slightly modified in each instance, consists essentially of division of the sternum, at the second or third interspace, transversely or somewhat obliquely from the second intercostal space to the third periosteal or third intercostal space (fig. 1). The internal mammary

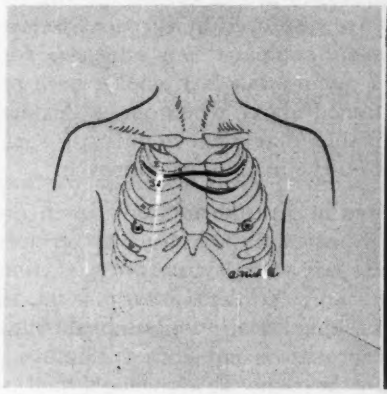

Fig. 1. Diagram of the anterior chest illustrating the course of transverse and oblique transsternal incisions employed for the exposure and excision of large anterior mediastinal tumors. The level of the incision may be altered to suit the case.

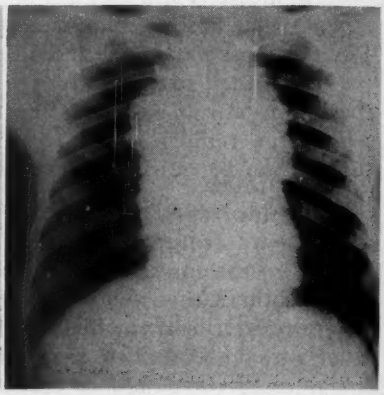

Fig. 2. Roentgenogram of the chest of patient No. 1 (R.M.) illustrating a large anterior mediastinal teratocarcinoma which was excised through a transverse transsternal incision at the level of the second interspace.

vessels are dissected free, doubly ligated and divided, and the pleurae are gently and bluntly reflected laterally. Occasionally tears of the thin pleura occur, which should be closed if possible. Positive pressure anesthesia through an endotracheal tube is indicated in each case, the patient being in the supine position. Catheter drainage of pleural spaces is carried out when the pleurae have been opened, inadvertently or purposefully. The sternum is reapproximated with two perichondral sutures of stainless steel wire (No. 30), one on each side of the sternum. In addition, fine silk sutures are placed in the anterior periosteum and fascia of the sternum.

Case Reports Illustrating Some of the Uses of Transverse Sternal Incisions:

Case 1. R. M., a 25 year old white male, was admitted to the hospital on Oct. 31, 1949, complaining of shortness of breath. The onset of the disease was believed to be in 1946 at which time he was said to have had tuberculosis, but which was later disproved on further examination. The patient had been hospitalized twice in the six weeks prior to the present admission for "upper respiratory infection" and dyspnea, at which times a tumor of the anterior mediastinum was first noted on roentgenologic examination (fig. 2). The tumor was considered to be a malignant lymphoma. Roentgen therapy to the anterior mediastinum failed to cause diminution of the size of the opacity,

visualized by roentgenologic examination. Axillary lymph nodes bilaterally removed for biopsy were noncontributory to diagnosis. The patient was referred for surgical exploration of the mediastinum with a tentative diagnosis of teratoma. On November 17, an exploratory thoracotomy and anterior mediastinotomy was carried out, utilizing a transverse transsternal incision at the level of the second interspace. An incarcerated mass measuring 12 by 8 by 4 cm. which on microscopic examination proved to be a highly anaplastic, necrotic, interstitial type of teratocarcinoma of the mediastinum. Postoperatively, there was no evidence of respiratory embarrassment, subjectively or objectively. Both lungs were well expanded. Pain was not a prominent complaint and the patient remained afebrile.

Six weeks after discharge from the hospital, the patient returned complaining of pain in the posterior chest wall. Roentgenologic examination revealed metastatic nodules of both lungs and metastases to the left posterior chest wall. Roentgen therapy and intercostal nerve blocks produced little relief. The patient died on Jan. 16, 1950. The postmortem diagnosis was interstitial type teratocarcinoma of the mediastinum with metastases to the lung, pericardial sac, ribs, and posterior chest wall. The surgical incision through the sternum was firm and well healed.

Comment: A transverse sternal incision was employed for the removal of a large malignant tumor, a teratocarcinoma. Firm union of the sternal incision was evident clinically and at postmortem examination two months later. In spite of the fact that the patient was not cured of his disease, the relative ease and safety of the surgical approach prompted its use in the following patient:

CASE 2. C. B., a 41 year old white male, was admitted to the hospital on Oct. 31, 1949, for surgical treatment of a traumatic contracture of the palm of the left hand and a lipoma of the left shoulder. Routine roentgenologic examination of the chest upon admission to the hospital revealed a smoothly-outlined mass occupying the medial half of the right upper chest (fig. 3). The mass, which displaced the trachea to the left, was nonpulsating on fluoroscopy. An esophagram demonstrated a deviation of the esophagus to the left and posteriorly by an anterior mass. Bronchoscopy revealed no abnormalities other than left tracheal deviation. Plastic procedures were performed on the hand, and the lipoma of the left shoulder was surgically removed. On Dec. 13, 1949, a mediastinotomy was performed through an oblique transsternal incision. The incision extended across the sternum from the right second intercostal space to the second rib on the left which was removed subperiostally. The right pleural space was opened and the left pleura was reflected laterally. The exposure revealed a large fatty tumor completely surrounding the right innominate vein. The entire mass was removed with the vein which in turn was ligated on the cardiac side of the junction of the right subclavian and internal jugular vein, and inferiorly, just above the junction of the right and left innominate veins. The surgical specimen measured 13 by 10 by 8 cm. and proved to be a lipoma of the mediastinum with no evidence of malignancy. Recovery of the patient was uncomplicated, except for a vague, dull headache which persisted postoperatively for about three weeks. He was free of symptoms when last seen two years following surgery.

Comment: The use of an oblique transsternal incision provided excellent exposure of the entire superior mediastinum and great vessels facilitating the removal of a large mediastinal lipoma together with the right innominate vein. Primary union of the sternum occurred with no postoperative respiratory difficulties.

CASE 3. B. S., a 42 year old white female, was admitted to the hospital on May 4, 1950, complaining of a "lump" of five months' duration in the right side of the neck. She complained also of some dyspnea, mild dysphagia and a 25 pound weight loss in three months.

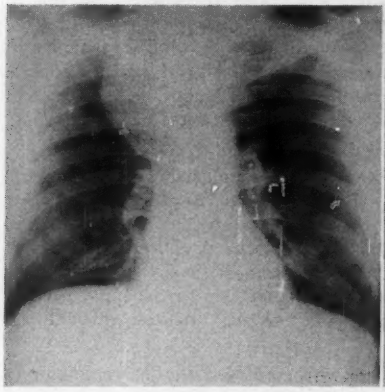

Fig. 3. Roentgenogram of the chest of patient No. 2 (C.B.) illustrating a large lipoma of the anterior mediastinum which had completely encircled the right innominate vein. The mass and the vein were completely excised through an obliquely situated transverse transsternal approach to the mediastinum.

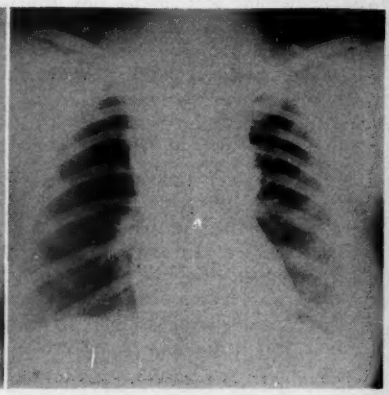

Fig. 4. Roentgenogram of the chest of patient No. 3 (B.S.) illustrating a large mediastinal Hodgkin's disease of the thymus gland. Partial excision through a transverse transsternal incision afforded tracheal decompression. Postoperative irradiation with x-ray caused the remaining tumor to disappear roentgenologically.

On physical examination a palpable mass which was present in both supraclavicular areas was thought to be continuous with a widening of the anterior mediastinum. There was no lymphadenopathy palpable in the axillary areas. Laryngoscopy was normal.

Roentgenologic examination demonstrated a large anteriorsuperior mediastinal mass, greater on the right than on the left, with deviation of the trachea to the left (fig. 4). Roentgenologic survey of the skeleton was normal. A tentative diagnosis of carcinoma of a substernal thyroid with minimal functional activity was suggested on the basis of clinical, roentgenologic and radioactive iodine studies. Through a transverse transsternal mediastinotomy incision (second intercostal space) a large mediastinal mass extending posteriorly to the vertebral column was found (fig. 5). The mass encircled the trachea, superior vena cava and aorta. Partial excision of the mass relieved the tracheal compression which was present. The pathological diagnosis was Hodgkin's disease of the thymus. Postoperative roentgen therapy to the mediastinum produced a reduction in size of the mass so that subsequent roentgenologic visualizations of the chest appear normal. The patient regained her normal weight and is free of symptoms 18 months following hospitalization. There is clinical roentgenologic evidence of nonunion of the sternal division which, however, causes no discomfort or respiratory difficulty in the patient.

Comment: This case illustrates the use of a transverse sternal incision for the partial excision of a mass with ensuing relief of tracheal compression produced by Hodgkin's disease of the thymus. Failure of the divided sternum to

heal primarily may possibly be due to the early postoperative use of roentgen therapy. In spite of the nonunion of the sternum there has been no respiratory dysfunction, a circumstance due to the fact that the greater portion of the sternum still serves as a fixed attachment for the ribs and thoracic musculature.

Fig 5. Photograph at operation of patient No. 3 (B.S.) illustrating the exposure of a large mediastinal mass through a transverse transsternal mediastinotomy incision. The superior component of the sternum swings anteriorly as if hinged by the sternoclavicular joints. Transmitted cardiac movement blurs the partially dissected tumor of the thymus.

Fig. 6. Angiogram illustrating superior vena cava distortion by indistinctly outlined metastatic renal adenocarcinoma in the anterior mediastinum. The surgical specimen, excised through an exploratory transverse transsternal incision measured 14 by 9 by 4 cm.

CASE 4. T. H., a 43 year old colored male, was admitted to the hospital on April 19, 1950. There was a history of dull pain of eight months' duration in the anterior chest. There appeared to be, on physical examination, a fullness in the right first intercostal space. Roentgenologic examination revealed an ill-defined mass in the anteriorsuperior mediastinum. An angiogram demonstrated distortion of the superior vena cava (fig. 6). A retrograde pyelogram showed a deformed right kidney pelvis. On May 19, 1950, a right nephrectomy for adenocarcinoma of the kidney was carried out with an uncomplicated recovery of the patient. On June 15, 1950, the anterior mediastinum was explored through a third intercostal transverse transsternal incision. A large tumor, 14 by 9 by 4 cm. was found to involve the posterior surface of the manubrium of the sternum, the first and second ribs, and the sternal heads of the clavicles. These structures were excised, utilizing the exploratory incision as the inferior margin of the excision. A bipedicled skin flap from the anterior chest was moved superiorly and the donor area was covered by split thickness skin grafts. Microscopic examination of the excised specimen was consistent with metastatic adenocarcinoma of the kidney. Postoperatively, there was no respiratory difficulty and the surgical areas healed primarily. The patient was well and without demonstrable recurrences when last seen 15 months from the time of mediastinal surgery.

Comment: The use of a transverse transsternal approach for anterior

mediastinal exploration provided good exposure for the removal of a large metastatic tumor of the mediastinum and anterior chest wall.

Discussion and Summary

A few cases are briefly presented to illustrate some of the uses of a transverse transsternal approach to the surgical management of large mediastinal tumors. The facility of this approach has been demonstrated also in the surgical exposure and treatment of large substernal goiters, aneurysms of the thoracic aorta, and congenital anomalies of the pulmonary artery. In one patient, after early postoperative roentgen therapy, there was noted a separation of the sternal margins allowing independent movement of the superior component. This circumstance in no way produces respiratory difficulty in this patient. The major portion of the sternum still affords anterior thoracic stability, so important in the function of respiratory movements. In all other cases in which the transsternal incision has been used the line of sternal approximation has been firmly united even on forceful pressure, and has exhibited primary healing. One of the patients has been observed for a period exceeding two years following surgery. In 1 case postmortem examination two months after the time of operation disclosed firm union of the sternal margins. The obliquity of the section of the sternum occasionally employed is thought to provide increased immobility of the sternum postoperatively. The transverse transsternal approach provides good surgical exposure for dissection of tumors from the great vessels of the mediastinum and allows the extirpation of large masses without rupture or surgical division. The safety of its use is due to the fact that the greater portion of the sternum is left intact for anterior thoracic stabilization. Its successful use is further insured by the careful employment of catheter drainage of pleural spaces which may have been opened.

The application of a transverse transsternal incision for the satisfactory excision of large anterior mediastinal tumors, as well as for other surgical conditions, has been found gratifying and worthy of renewed popularity.

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BLOOD VOLUME DURING LOW SPINAL ANESTHESIA*†

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PROVISION of optimal working conditions for the surgeon is one component of ideal anesthesia. Equally important is the maintenance, or restoration of normal physiology, in each patient. Among numerous physiologic derangements that may demand attention, blood volume has aroused renewed interest in the past few years. While the literature contains a number of reports of clinical studies of blood volume in various conditions, very little data are available concerning the effects of spinal anesthesia on the circulating blood volume in man. The importance of this problem was strikingly demonstrated by preliminary blood volume studies which we made upon 2 patients receiving spinal anesthesia (Pontocaine 5 mg. in 0.8 cc. of 10 per cent glucose solution). The level of anesthesia was confined to the tenth thoracic dermatome segment. The first patient showed a decrease in blood volume of 15 per cent, and the second patient a decrease of 5 per cent below average normal before spinal anesthesia. Ten minutes after the subarachnoid injection of the agent, and before the start of the surgical procedure, circulatory collapse occurred in both. These 2 cases required vasopressor drugs, blood and oxygen therapy. Surgery was cancelled in the first patient and allowed to proceed in the second. The first patient was subsequently operated upon under pentothal-nitrous oxide anesthesia.

Since patients about to undergo surgery may have already altered blood volume from a variety of causes (*e.g.*, dehydration, hemorrhage, malignancy, cardiovascular disease or malnutrition) it is important to know if the anesthetic will further alter this value, and the magnitude and direction of change that may be anticipated. For example, a patient with a blood volume distinctly below normal is already compensating for this, but may be unable to meet any increased demand; therefore, one should not select an anesthetic that might further reduce the blood volume without taking steps to correct the deficiency. The following studies were undertaken to determine the effects of low spinal anesthesia on blood volume.

Forty-nine cases are presented. These are shown graphically in chart 1. One hundred and fifty determinations of blood volume

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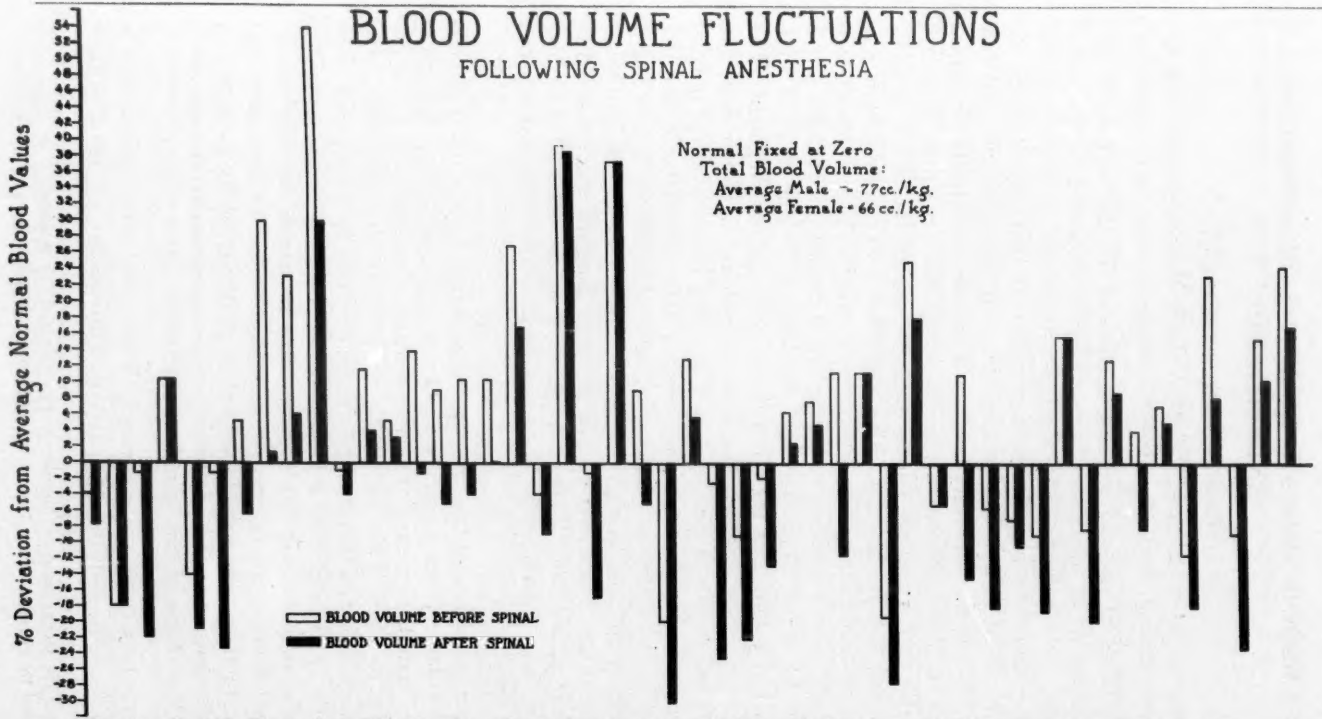
BLOOD VOLUME FLUCTUATIONS
FOLLOWING SPINAL ANESTHESIA
Normal Fixed at Zero
Total Blood Volume:
Average Male = 77cc./kg.
Average Female = 66 cc./kg.
% Deviation from Average Normal Blood Values
BLOOD VOLUME BEFORE SPINAL
BLOOD VOLUME AFTER SPINAL

Chart 1. Graphic illustration of blood volume fluctuations in 49 cases before and after subarachnoid anesthesia. The white blocks are the blood volume before and the black blocks after anesthesia.

were made. Other cases are omitted from this discussion chiefly for two reasons: (1) technical errors were inevitable in many of the earlier determinations, while the method was being adapted to the routine of a busy surgical clinic; and (2) throughout the series, a certain percentage of patients required therapy which made blood volume values difficult to interpret because of the variable factors introduced. All patients were elderly males who received low spinal anesthesia prior to transurethral prostatic resection. Their ages ranged from 49 to 86 years, distributed as shown in table 1.

TABLE 1

Age	*No. of cases*
49 years	1
50-59 years	4
60-69 "	11
70-79 "	27
80-86 "	6

Procedure

Following premedication, consisting in most cases of vin-barbital sodium [sodium 5 ethyl 5 (methyl 1 butenyl) barbiturate] (0.1 Gm.) one and one-half to two hours preoperatively, and atropine sulphate (0.4 mg.) with either morphine sulphate (8 mg.) or demerol (50 to 100 mg.). One hour preoperatively the patient was brought to the anesthesia induction room and an initial sample of blood was drawn for volume determination. Spinal anesthesia was then administered with the patient in the sitting position. Seven mg. of pontocaine hydrochloride in 1 cc. of 10 per cent dextrose was the agent used in all cases. Injection was made slowly into the third or fourth lumbar interspace without barbotage. The patient was kept in the sitting position for two minutes following the pontocaine injection. Four to six additional samples were taken for blood volume determinations following administration of the spinal anesthetic. These were withdrawn at 10 minute intervals. In some cases technical problems (*e.g.*, difficulty in venipuncture) caused deviation from the exact interval, but in all cases time was noted with a stopwatch, and calculations were based on the actual interval. Methamphetamine hydrochloride (methedrine 20 mg.) was given to avert or correct hypotension in those cases judged to require a vasopressor. No significant quantities of fluids were administered intravenously before all samples for blood volume determination had been obtained. A normal saline infusion was regulated to drip at 5 to 10 drops per minute, introducing a maximum volume of 60 cc. per hour, to keep a 20 gauge needle patent. The majority of the determinations were completed before the opera-

tive procedure had progressed very far, and in none of the cases included was there clinical or objective evidence of significant hemorrhage before all samples for the study had been obtained. The results, therefore, should be indicative of the effect of low spinal anesthesia upon blood volume.

Method

Plasma volume was determined by injecting intravenously the Evan's Blue dye (the Sodium salt of tollidine-di- (1-amino-8-napthol- 2:4-disulphonic acid) as originally described by Gibson and Evans[1] and subsequently modified for use with the photoelectric colorimeter.[2] Serum proteins, hemoglobin and hematocrit were determined on all samples, and the latter value used to calculate red cell volume and total blood volume according to the formulas:

1. $\frac{LV}{F}$ = cc. dye in 1 cc. plasma (where L is a photometer reading corresponding to the negative logarithm of the optical density, V is the concentration of the dye, and F is the standardization factor of the dye)
2. Total plasma volume $= \frac{\text{cc. dye injected}}{\text{cc. dye in 1 cc. plasma}}$
3. Total blood volume $= \frac{\text{Total plasma volume}}{(100 - \text{hematocrit})} \times 100$
4. Total red cell mass = Total blood volume—Total plasma volume

Results

Following induction of spinal anesthesia, 43 of 49 cases (87 per cent) had a decrease in blood volume of from 1 per cent to 30 per cent below the volume as determined immediately prior to anesthesia. These were subdivided as shown in table 2. Six of 49 cases (12 per cent) had no change in blood volume following induction of spinal anesthesia.

TABLE 2

Decrease in Blood Volume	*No. of Cases*
1% to 5%	11
6% to 10%	11
11% to 15%	12
16% to 30%	9

In this series, 32 cases had no operative or postoperative complications. Of these, following administration of spinal anesthesia:

6 cases had no change in blood volume
9 cases had a decrease in blood volume of 1% to 5%
8 cases had a decrease in blood volume of 6% to 10%
6 cases had a decrease in blood volume of 11% to 15%
3 cases had a decrease in blood volume of 16% to 22%

There were three postoperative deaths. Two of these patients had a 14 per cent decrease in blood volume following induction of anesthesia; the third had a decrease of 25 per cent.

Five cases having operative or postoperative complications had decreases in blood volume following induction of spinal anesthesia as follows:

2% AV Block in the immediate postoperative period. (Coronary insufficiency had been diagnosed preoperatively.)

11% Postoperative hemorrhage and prolonged convalescence.

12% Cerebrovascular accident on sixth postoperative day.

15% Marked but asymptomatic hypotension during and after surgery.

24% AV Block in the immediate postoperative period (Emphysema arteriosclerotic heart disease with minimal decompensation diagnosed preoperatively).

Seven cases had no operative or postoperative complications, but had clinical evidence of cardiac decompensation preoperatively. These gave the following values:

TABLE 3

Per cent Deviation from average normal blood volume

Before Anesthesia	*After Anesthesia*	*Decrease*
+ 31	+ 1	30%
+ 13	+ 5	8%
+ 8	+ 5	3%
+ 11	— 12	23%
+ 25	+ 18	7%
— 6	— 18	12 %
— 8	— 20	12 %

The 2 remaining cases had no operative or postoperative complications, but are of interest:

Case 6 had arteriosclerotic and hypertensive heart disease with moderate decompensation. Original blood volume was 2 per cent below average normal, with a 20 per cent drop following anesthesia. Surgery had previously been deferred in this patient when, two days prior to the operative procedure, circulatory collapse had ensued immediately following induction of spinal anesthesia. Unfortunately, blood volume determination was not made before the first anesthesia.

Case 9 was found to have chronic lymphatic leukemia. The original blood volume was 2 per cent below average normal, with a 20 per cent drop following anesthesia.

Blood volume values in this series showed poor correlation with values for hemoglobin, hematocrit, and serum proteins.

Discussion

The results of this, or any blood volume study, are much less easily evaluated than might be inferred from superficial consideration of the problem. It therefore seems apropos to preface any discussion with a summary of the more important variables:

"Normal" values: Elsewhere in this paper the expression, "average normal blood volume," is used to denote 77 ml./Kg. of body weight. This usage is in keeping with recent values given in the literature for the method employed.[3,4,5] However, it must be realized that this is an approximation. "Normal" values quoted throughout the literature vary widely. For any given article it is necessary to ascertain what values are assumed as normal before comparing it with similar studies. The first edition of Best and Taylor[6] gives the normal value as 90 ml./Kg.; in the present (third) edition it has dropped to 78 ml./Kg. At least one recent study[7] assumes a normal value as high as 85 ml./Kg. A basic reason for the variation appears to be the fact that blood volume is more directly a function of surface area than of body weight.[3,8,9] Of numerous other reasons[8,10,11,12,13,14,15,16] some are obvious, others less so. In any case, a discussion of them is beyond the scope of this paper.

Methods

As Gregersen[12] has pointed out, there is no longer much foundation for the view that no method is valid simply because all do not give identical values. Measurement of blood volume has proved clinically useful although few contend that any present method measures the true volume.[17] Knowledge of the limitations of various procedures is prerequisite to comparing their results. Values for total blood volume as determined by the plasma dye T-1824 average 12 per cent higher than those given by methods employing radioactive isotopes (Fe^{55}, P^{32}) to tag erythrocytes.

Numerous physiologic and pathologic processes which may alter blood volume in a given case must be evaluated.[3,10,18,19,20,21,22,23,24,25,26,27]

While knowledge of the mechanism which maintains blood volume within normal limits is incomplete, factors concerned include:

1. Maintenance of red cell volume by erythropoiesis, erythrocyte destruction, and splenic functions.

2. Maintenance of plasma volume by fluid and solid intake, adjustment of electrolyte output (primarily renal), and exchanges between vascular and interstitial fluid due to fluctuations in hydrostatic and osmotic pressures.

3. Maintenance of the ratio between total blood volume and capacity of the vascular bed by vasomotor nerves, hormonal and chemical influences, and physical forces intrinsic in the vascular structure.[28,29]

Blood is not merely the transport medium for the organism; its ultimate function is to provide cellular environment optimally suited to metabolic activity. Life processes require that this environment be stabilized within narrow limits, especially in respect to temperature, hydrogen ion concentration, and osmotic pressure. The importance of maintaining blood volume within physiologic limits stems from its relation to these phenomena. In determining the limits within which blood volume may vary without endangering normal metabolism, one must know the fluid balance of the body. Gamble's classical work[20] divides body water into vascular, interstitial and intracellular compartments. Balance is maintained by osmotic pressure differences, and is thus dependent primarily on plasma proteins, sodium ions and potassium ions in the respective compartments. Because of their vital functions, vascular and intracellular fluids are supported at the expense of interstitial fluid. When the latter is seriously depleted, additional reductions of plasma volume, however small, may endanger vital functions.

Analysis of the results in the 49 cases studied suggests the following, although no claim is made for statistical significance:

Spinal anesthesia decreases blood volume in the majority of patients.

Despite considerable recent work on blood volume in surgical patients,[7,30,31,32,33,34,35,36] only that of Guest, Mann and Searles[37] is directly concerned with its relation to spinal anesthesia. They state: "A search of the literature failed to reveal any studies on blood volume and spinal anesthesia in man." Twenty-five patients of these authors undergoing a variety of surgical procedures were studied. Determinations were made several days before anesthesia and again 10 to 15 minutes after anesthesia. In the majority of cases, blood and plasma volume showed insignificant changes. There was a rise in blood and plasma volume in a small percentage of cases.

The above results appear to directly contradict those of the present study. No entirely adequate explanation for this is offered, but the following merit consideration: (Series G indicates the cases of Guest et al.: Series L, this study.)

(a) Average age of patients:
Series G: 37.5 years; Series L: 71.8 years

(b) Position during subarachnoid injection:
Series G: lateral recumbent; Series L: sitting

(c) Possible effect of the intrathecal ephedrine[38] used in Series G

(d) The difference may be apparent rather than real, due to the small number of cases in both series, and to interpretation. In Series G a change of volume less than 450 cc. is considered insignificant. This is approximately 8 per cent of their value for total average blood volume. If the same criterion be applied to our series, the two compare as follows (table 4):

TABLE 4

Series G *25 Cases*	Series L *49 Cases*
6 patients had rise above 8%	0 patients had rise
13 patients had rise below 8%	.....
6 patients had fall below 8%	25 patients had fall less than 8%
.....	24 patients had fall more than 8%

In Series G, the reason given for considering 450 cc. as the significant figure is that values below this were within limits of error of the method used (T-1824). While this may be valid in this particular instance, any generalization as to the amount of blood volume that a patient can lose "without significance" is potentially dangerous. This varies widely depending upon the state in which an individual comes to surgery; a 1 per cent loss in a debilitated patient may be more significant than a 10 per cent loss in the average patient.

It is noteworthy that no question of "normal" values is involved here; in both series the altered blood volume is considered in relation to a previous value in the individual. However, the fact that the original determinations were done several days prior to anesthesia in Series G, as compared with 10 minutes prior in Series L, may be of significance.

Decrease in blood volume of appreciable degree is associated with increased mortality and morbidity. Although some of these patients were able to compensate for decreased blood volume to the extent of 20 per cent to 30 per cent it must be noted that the three deaths and five instances of postoperative complications occurred, with one exception, in that group having a decrease in excess of 10 per cent. This is confirmed by other studies[7,30,39,40] which stress the importance of specific replacement therapy in the preoperative preparation of patients. Hero and Barber,[39] from determinations of pre- and postoperative values, conclude: "Elderly surgical patients may be protected against cardiopulmonary death and peripheral vascular collapse only by careful studies which

should include blood volume, hematocrit, and serum proteins." They particularly emphasize the role of normal plasma proteins in the prevention of pulmonary edema. Jensen et al.[40] found that postoperatively diminished blood volume was associated with wound dehiscence in 40 cases.

Values for plasma proteins, hemoglobin and hematocrit showed poor correlation with those for blood volume. This finding is in agreement with the work of other investigators[7,16,19,34,40] who have shown that the former values often give an erroneous picture of the circulating volume. Gain or loss of weight is frequently a better clinical guide than plasma proteins, hemoglobin and hematocrit in cases where blood volume cannot be determined.

Gamble[20] cites experimental work to demonstrate that the plasma protein level may remain unchanged for 10 days following the onset of gradual dehydration and weight loss. However, at the end of this 10 days period, there is a marked rise in the concentration of plasma proteins coincident with rapid reduction of plasma volume.

The effect of spinal anesthesia on blood volume is intimately related to its effect on blood pressure. The arterial hypotension so frequently seen with this anesthetic technic is contributed to by a number of factors[41,42,43,44,45,46,47,48,49,50,51,52] principally: (a) Loss of vasomotor tone due to paralysis of vasoconstrictor fibers in the anterior nerve roots; (b) Loss of skeletal muscle tone; (c) Respiratory depression depending on the height of anesthesia, and due usually to intercostal paralysis; (d) A lack of compensatory reflexes not entirely explained by (a) e.g., Heyman's demonstration that carotid sinus depression occurs when sensory anesthesia is at the level of the umbilicus.

Many workers place major significance on the factor of arteriolar dilatation in causing hypotension;[53] however, Smith, Rovenstine et al.[45] have postulated that the basic mechanism is a decreased venous return due to loss of skeletal muscle tone and resulting dilatation of capillaries, venules, and veins.

It seems most probable that arteriolar dilatation occurs in the anesthetized area; however, this per se does not explain decreased blood volume. Little, if any, exchange of fluid between the intravascular and interstitial compartments occurs through the walls of the larger vessels. On the other hand, decreased venous return and resultant capillary dilatation could well account for the diminution in volume, since transfer of fluid from blood vessels to tissue spaces is facilitated by (a) increased filtration pressure due to the increased

hydrostatic pressure; and (b) increased capillary permeability due to decreased circulation rate.

Summary

In a study of 49 patients, 87 per cent had decreased blood volume, and 12 per cent had no change in blood volume following induction of spinal anesthesia.

Marked reduction in blood volume is associated with an increased mortality and morbidity.

A comparison of these results with others reported in the recent literature is made.

Mechanisms relating diminished blood volume to arterial hypotension are discussed.

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POSTERIOR GANGLION AT THE ANKLE: A CASE REPORT*

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THIS report is submitted because the patient was found to have a ganglion, similar to those frequently seen about the wrist and less frequently in other locations, in an area where the occurrence of this lesion is apparently extremely rare. A search through the Index Medicus under appropriate titles back to 1916 has failed to identify a previously reported ganglion similar in location to this one.

A five year old white male child was seen in June, 1951, the presenting complaint being that the parents had noted a swelling behind the left ankle for the previous six months. This had been discovered after it had been noted that the child would frequently remove his shoe from that foot. It was the impression of the parents that the mass had steadily increased in size. The ankle was apparently not extremely painful, but it had been noted that he tended at times to walk on his left toes.

The birth and early development of the child was normal except that he had great difficulty with speech and had been under treatment for this. His intelligence was considered normal but he had an auditory aphasia. Past medical illnesses were not unusual except for the fact that at the age of 3½ years he had a severe reaction several days after receiving tetanus antitoxin. The family history was negative. The child had a normal younger sister.

The physical examination disclosed a healthy appearing boy with an obvious speech defect, sufficient to make it extremely difficult to communicate with him. Intelligence otherwise seemed normal. The general examination was negative. Orthopaedic examination was normal except for the presence of a visible and palpable mass about 1 inch in diameter which could be felt on each side of and anterior to the left Achilles tendon at the level of the medial malleolus. This mass felt like a cyst and was movable within the confines of its anatomical location laterally. When pressed upon from either side of the Achilles tendon it would become more prominent on the opposite side. It did not seem to be attached to the skin or to the Achilles tendon, and attachment to deeper structures was not demonstrable. Roentgenograms of both ankles showed, on the left, a soft tissue mass beneath the Achilles tendon (fig. 1). Routine laboratory

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work was within normal limits. In view of its increasing size and uncertain nature, excision was advised.

Fig. 1. Roentgenograms of both ankles. The outline of the mass has been emphasized with broken lines.

Fig. 2. Photograph of ganglion prior to removal of the pedicle.

With the patient in prone position under general anesthesia, and without a tourniquet, a 3-inch posterior incision was made lateral to the Achilles tendon, running proximally from its insertion. The

tendon was retracted medially and the mass, which was about 1½ inches in diameter and covered with a heavy capsule which blended into surrounding structures, was identified (fig. 2). By careful dissection, the mass was removed with its capsule. The capsule was quite vascular and the use of a tourniquet would have made the procedure much easier. The capsule was adherent to the peroneus brevis and flexor hallucis longus. The mass was found to have a pedicle which was followed down and found to be intimately adher-

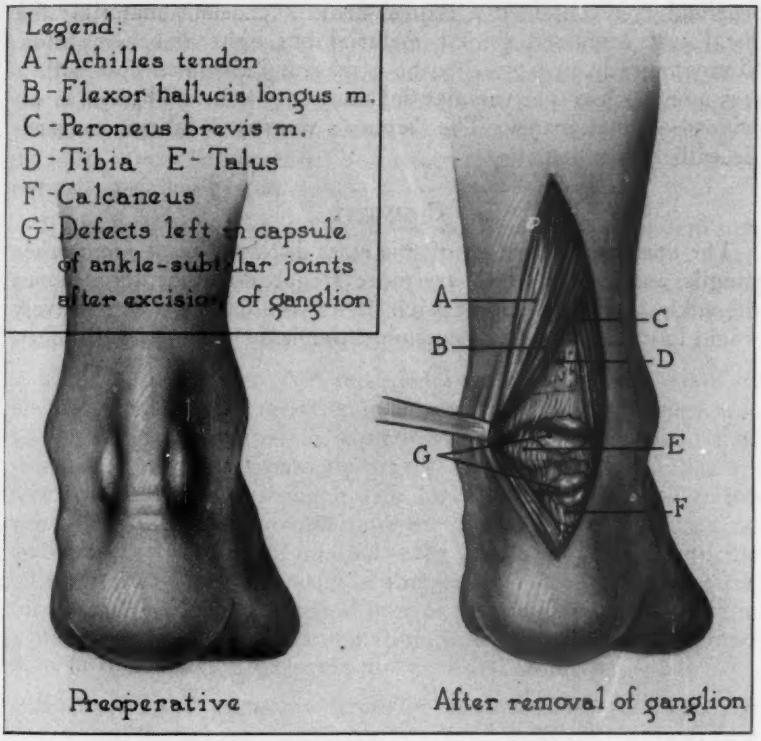

Fig. 3. Artist's drawing made from rough sketches supplied by the author.

ent to the inferior tibio-fibular ligament, and to the capsule of the posterior ankle and subtalar joints. The mass and pedicles were removed. The dissection of the involved deeper structures amounted to a partial posterior synovectomy of both the ankle and subtalar joints (fig. 3). The gross appearance of the mass was typical of a ganglion, or in an appropriate location, a Bakers cyst. The joint capsules were left open, the wound was otherwise closed in layers and a plaster cast applied from the tibial tubercle to the

base of the toes, with the foot in moderate equinus. The patient was left in the plaster cast for three weeks and then permitted weight-bearing with a 5/8-inch heel extension on the left shoe. This was removed after an additional four weeks, and at five months postoperatively there was no evidence of recurrence.

On opening the specimen, the mass proved to be cystic and biocular with a pedicle running down to both the ankle and subtalar joints, but apparently not communicating with either of them. The proximal cyst contained a reddish-brown, tenacious material; the distal cyst contained similar material but light amber in color. Microscopically, it proved to be a mesothelially-lined cyst with a few mononuclear perivascular inflammatory cells. There was no evidence of malignancy. The diagnosis was: synovial cyst compatible with a ganglion.

Comment

The anatomical location of this mass distinguishes it from other ganglia and bursae which are more frequently encountered about the ankle joint. An appreciation of its true nature preoperatively would have expedited the excision through the use of a tourniquet.

THE VASCULAR RESPONSE OF THE STOMACH TO EXPERIMENTAL ALTERATIONS IN THE AUTONOMIC NERVOUS SYSTEM OF THE DOG

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RENEWED contemporary interest in the relationship between the autonomic nervous system and gastric function, especially concerning the pathogenesis and treatment of peptic ulcer, directs attention to the vasomotor response of the stomach to alteration of the nerve supply to this organ. It has been shown that the occurrence of peptic ulceration, although primarily due to acid-peptic ulceration, may be influenced by various circulatory changes experimentally produced in animals.[1]

It has long been known that the sympathetic nervous system supplies vasoconstrictor fibers to the abdominal viscera;[2] that a small number of vasodilator fibers also exists in the splanchnic nerves was shown by Bülbring and Burn.[3] Evidence of vagal vasomotor influence on the intestinal tract has not been consistent.

Lim, Necheles, and Ni[4] recorded combined measurements of blood flow and gastric secretion in animals in which the stomach was vivi-perfused and placed in a plethysmograph. They found that stimulation of the sympathetic nerves accompanying the celiac artery produced vasoconstriction with diminution of blood flow to the stomach. Adrenalin injected into the perfusor dog produced no uniform effect, but when injected, even in minute dosage, into the celiac artery of the vivi-perfused stomach produced a vasoconstrictor effect or reduction in blood flow as measured volumetrically in a plethysmograph. Vagal stimulation produced no vasomotor reactions in the acutely denervated vivi-perfused stomach.

Burton-Opitz,[5] using the stromühr method in the anesthetized dog, found that vagus stimulation produced no effect on blood flow other than inhibition when strong peristalsis was excited. Stimulation of either the splanchnic or the postganglionic fibers on the gastrolienal vessels produced a decrease in the blood flowing through the splenic vein of the anesthetized animal.

The color of the intestinal mucosa has been used as an indication of the state of blood flow in animals and man. Wolf and Wolff[6]

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correlated changes in blood flow, acid production and motor activity accompanying various emotional states to show that an increase in one was associated with an increase in the other.

Accelerated blood flow to the stomach and duodenum in man accompanying emotional anxiety, tension, and resentment may occur as shown by measurement of blood flow by means of a thermal gradientometer.[7]

Experiments in the present study have been devised to measure, in a simple manner, relative changes in blood flow to the stomach in intact and unanesthetized dogs. These are studies in which the autonomic nerves are chronically stimulated, separately over long intervals of time, or in which the nerves have been previously surgically divided or excised.

Method

Healthy adult dogs were used in this study. Those dogs in which stimulation of the vagus and/or sympathetic nervous system was carried out were prepared by placing, under aseptic surgical conditions, a pair of electrodes as described by Kubicek and Kottke[8] upon the nerves to be stimulated. In the case of the vagus nerves, an electrode was placed on each of the two vagal trunks by the transthoracic approach and led out through the chest wall. Larger electrodes were placed on the caliac axis and on the left gastric artery, respectively, care being taken not to injure, or divide the sympathetic nervous plexus at these sites. All animals so prepared were allowed to recover for one to three months before studying the vascular response of the stomach to stimulation via the preplaced electrodes. After complete recovery of the animal, studies were made consecutively before stimulation, during stimulation, and after stimulation without altering or adjusting the experimental apparatus or conditions.

Three consecutive studies of vascular flow to the stomach were carried out in each of another group of healthy adult dogs before division or excision of the autonomic nerves. The vagal trunks were divided with excision of 2 cm. of nerve tissue under aseptic surgical conditions using a left transthoracic approach. The celiac ganglia and postganglionic fibers of the branches of the celiac axis were excised under sterile surgical conditions through a midline or left subcostal abdominal incision in another group of healthy adult dogs previously studied for vascular flow to the stomach. All dogs were allowed to recover completely for a period of one to three months before studying the effect of excision of these nerves on the blood flow to the stomach.

Relative changes in blood flow to the stomach during and after stimulation or before and after excision of the vagus and sympathetic nerve supply to the stomach were determined using a simple device consisting essentially of gradient thermocouples placed in an intact nonanesthetized experimental dog. One thermocouple was situated on the inner surface of the gastric mucosa, another within a thin rubber balloon placed in the stomach containing a known volume of water at a known initial temperature, and a reference thermocouple placed in the rectum of the animal. Readings from a calibrated galvanometer were noted at intervals of one minute until equilibrium was reached.

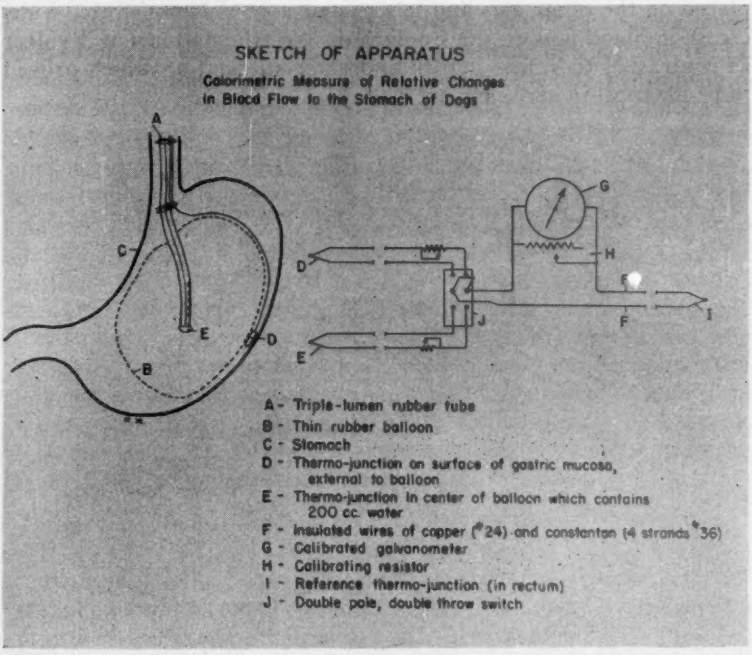
SKETCH OF APPARATUS
Colorimetric Measure of Relative Changes in Blood Flow to the Stomach of Dogs
A
B
C
D
E
G
H
I
J
F
A - Triple-lumen rubber tube
B - Thin rubber balloon
C - Stomach
D - Thermo-junction on surface of gastric mucosa, external to balloon
E - Thermo-junction in center of balloon which contains 200 cc. water
F - Insulated wires of copper (#24) and constantan (4 strands #36)
G - Calibrated galvanometer
H - Calibrating resistor
I - Reference thermo-junction (in rectum)
J - Double pole, double throw switch

Fig. 1

Insulated wires from the thermocouples were run via a triple-lumen rubber tube to the calibrating apparatus and galvanometer. The rubber tube was placed through the mouth of the dog so that the balloon was situated well in the stomach—the reference electrode in another insulated rubber tube previously placed in the rectum. Two hundred cc. of water at 20 C. was run into the balloon as rapidly as possible and readings taken immediately, and every minute until equilibrium was reached. Calibrated readings indicated

the difference in degrees of centigrade temperature of the water in the gastric balloon and the rectum. The time at which equilibrium was reached indicated the state of blood flow—an increase in time representing a decrease in flow to the organ, and vice versa. It should be understood that actual quantitative determinations of blood flow per second are impossible by this—a calorimetric method, but that relative changes in flow under varying conditions are readily recognized by the varying time to reach equilibrium (fig. 1).

Results

The three dogs in which electrodes had previously been surgically placed on the celiac axis and left gastric artery demonstrated a decrease in blood flow to the stomach during stimulation (of 3 volts) as contrasted to values before and after stimulation which proved to be identical in each instance (fig. 2).

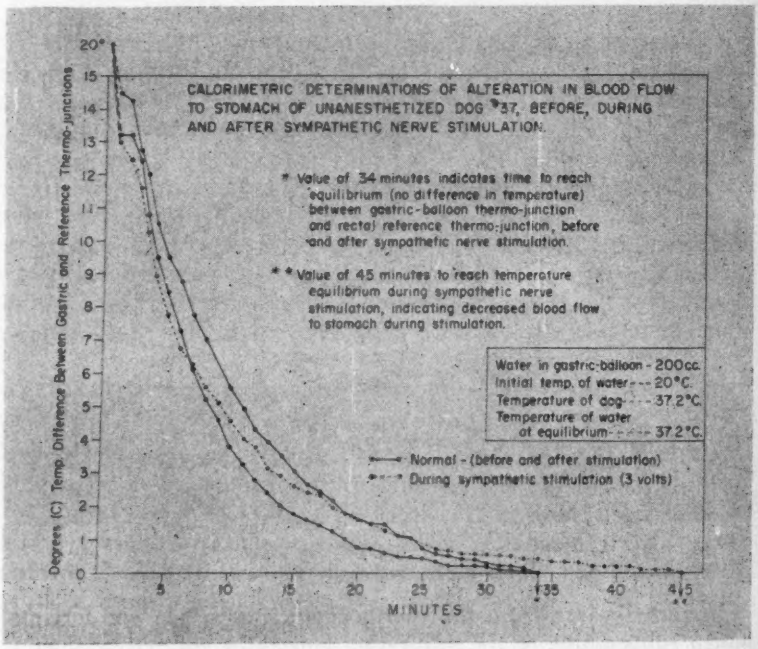
CALORIMETRIC DETERMINATIONS OF ALTERATION IN BLOOD FLOW TO STOMACH OF UNANESTHETIZED DOG #37, BEFORE, DURING AND AFTER SYMPATHETIC NERVE STIMULATION.
* Value of 34 minutes indicates time to reach equilibrium (no difference in temperature) between gastric-balloon thermo-junction and rectal reference thermo-junction, before and after sympathetic nerve stimulation.
** Value of 45 minutes to reach temperature equilibrium during sympathetic nerve stimulation, indicating decreased blood flow to stomach during stimulation.
Water in gastric-balloon - 200cc.
Initial temp. of water - - - 20°C.
Temperature of dog - - - 37.2°C.
Temperature of water at equilibrium - - - - 37.2°C.
Normal - (before and after stimulation)
During sympathetic stimulation (3 volts)
Degrees (C) Temp. Difference Between Gastric and Reference Thermo-junctions
MINUTES

Fig. 2

There proved to be no alteration in blood flow to the stomach upon vagus nerve stimulation in 2 unanesthetized dogs having electrodes on the vagus trunks. The values before and after stimulation were equal to those during stimulation.

The blood flow to the stomach remained essentially unchanged after celiac ganglionectomy in 3 dogs when studied from seven days to six months following surgery.

There was no significant change in the blood flow to the stomach following transthoracic vagotomy in 2 dogs studied one to six months following surgery. A few experiments indicated a tendency to decreased flow but these changes were not significant nor uniform.

Determinations were repeated in each dog in each category of experimental conditions.

Discussion

Experimentally this method of studying blood flow to the stomach allows one to determine relative changes brought about by various conditions. From these studies it appears that the vasomotor response in the stomach of the dog is influenced primarily if not solely by the sympathetic nervous system, demonstrated by the decrease in flow upon sympathetic nerve stimulation. Additional observations regarding the effect of sympathetic nerve stimulation were made in these animals by gastroscopy and direct visualization of the gastric mucosa by gastrotomy in anesthetized dogs. It was noticed that upon sympathetic nerve stimulation there occurs a transient and barely recognizable pallor of the mucosa which gives way in two to three minutes to a deeply engorged and congested mucosa, cyanotic in appearance, which persists during stimulation. No such demonstrable changes were noted upon vagal nerve stimulation. The changes noted may take place also in the nonanesthetized dog which would be consistent with the findings of decreased blood flow by the calorimetric method.

Conclusions

A simple method of studying alterations in gastric blood flow in the intact and nonanesthetized animal is presented. By the employment of a calorimetric apparatus it is demonstrated that the blood flow to the stomach is reduced in dogs during sympathetic nerve stimulation carried out over prolonged intervals of time. No appreciable alterations in gastric blood flow occur upon vagal nerve stimulation performed under similar conditions or following excision and division of either the sympathetic or vagal nervous system by the method described herein.

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RECONSTRUCTIVE METHODS FOR SURGICAL DEFECTS OF THE CHEST WALL

Including the Use of Pre-formed Lucite Plates

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THE ever widening scope of thoracic and radical tumor surgery has focused greater attention on the management of surgical defects of the chest wall. Large defects of these soft and bony parts require major reconstructive procedures. Ideally, these procedures afford primary wound closure and stability of the chest wall, without involving lung collapse or other major distortion. Internal prostheses are often indicated, particularly in anterior and lateral defects of the thoracic cage. External stabilizing appliances have usually been found unsatisfactory.[1]

Numerous methods have been described for securing a stable closure of bony defects of the chest wall. As early as 1909 Gangolphe and Tixier[2] proposed the use of a metal prosthesis to reconstruct the resected sternum. Janes[3] used a pedicled rib graft, obtained by sawing an adjacent rib lengthwise, and displacing one fragment downward. Internal rotation of the pectoralis major muscle provided a smooth contact surface for the lung. Maurer and Blades[4] have reported the use of periosteal flaps elevated from adjacent ribs. Kinsella et al.[5] reconstructed a sternum by means of a long tibial bone graft, while Bisgard and Swenson[6] suggested mortised rib grafts for this same purpose. Fascia lata strips were employed by Watson and James to close chest wall defects in 4 patients.[7] Beardsley[8] obtained chest wall stability in 3 patients by utilizing tantalum plate, but recently Ada and Hevenor[1] have indicated that tantalum mesh is superior to the solid sheet. Extensive thoracoplasty[9] has been commonly used to secure closure of chest wall defects, but has the obvious disadvantage of causing lung collapse with impaired ventilation.

CASE REPORTS

CASE 1.† R. M., a 51 year old white male, gave a history of two years' duration of a rapidly enlarging huge tumor of the left anterior chest wall

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†Cases 1 and 3 were operated on by one of us (P.W.S.) at the University of Chicago Clinics, Chicago, Illinois.

which had been treated ineffectively by repeated courses of roentgenotherapy (fig. 1). The patient first discovered this tumor in an area of contusion which he had sustained in an automobile accident a few days before. This observation is of interest in the light of a similar history obtained from his mother (case 3). Roentgenologic studies of the chest showed the tumor to have a large intrapleural extension with destruction of the anterior segments of the second and third ribs (fig. 2a).

Fig. 1. Photograph of patient described in case 1 (neurogenic sarcoma) illustrating the huge size of this tumor, its nodularity, and the overlying atrophic, telangiectatic skin.

On June 26, 1945, he was subjected to a radical full-thickness resection of the left anterior chest wall. The specimen measured 20 by 30 by 15 cm. and included anterior segments of the second, third, fourth and fifth ribs. His-

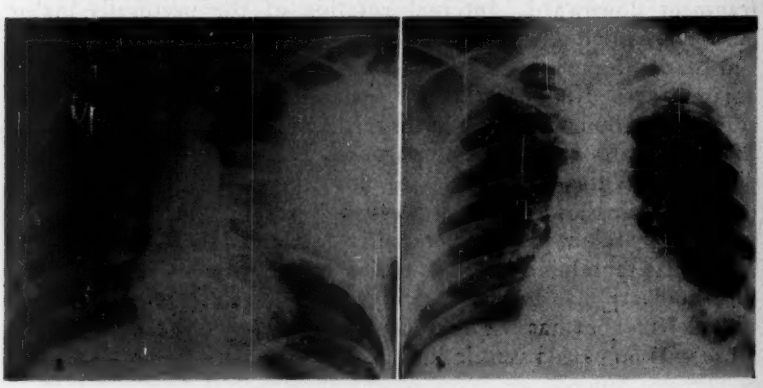

Fig. 2a. Preoperative roentgenogram of patient in case 1 showing extent of involvement of the left chest.
b. The film postoperatively reveals the surgical defect.

tologically, the tumor was a neurogenic sarcoma. A huge bipedicled flap, anchored in the interscapular and the right groin areas, was used to cover this major defect, the large donor area being covered with split-thickness grafts. The patient quickly responded from the operation and gained 60 pounds in weight during the latter half of 1945 (fig. 2b).

In spite of various types of padded external supports he experienced difficulty with paradoxical motion of his unstable chest wall and it was the observation of this functional defect that stimulated our use of rigid internal plates. However, in January, 1946, he had developed diffuse bilateral pulmonary metastases and rapidly became worse and died in February, 1946.

Comment: Our approach to providing stability in large defects of the thoracic wall has been the use of various synthetic plastics, particularly Lucite, and more recently Fibreglas. Lucite is a methyl methacrylate resin, also termed Crystalite and Plexiglas. It is colorless, transparent, and thermoplastic (100 C. to 120 C.). It has the advantages of complete functional stability, satisfactory tissue tolerance, and radiolucency. It has the slight disadvantages of requiring preoperative cutting, shaping, drilling of holes for suturing, and of cold sterilization.

The following cases illustrate restoration of stable continuity of the chest wall with primary closure and without lung collapse.

CASE 2. E. M., a 41 year old female, on examination, was found to have an ulcer with rolled margins in the medial end of a left radical mastectomy scar (fig. 3a). This operation had been performed elsewhere in 1943 and the patient had received postoperative roentgenotherapy, her skin bearing the stigmata of massive irradiation sequellae. On May 11, 1950, she underwent a

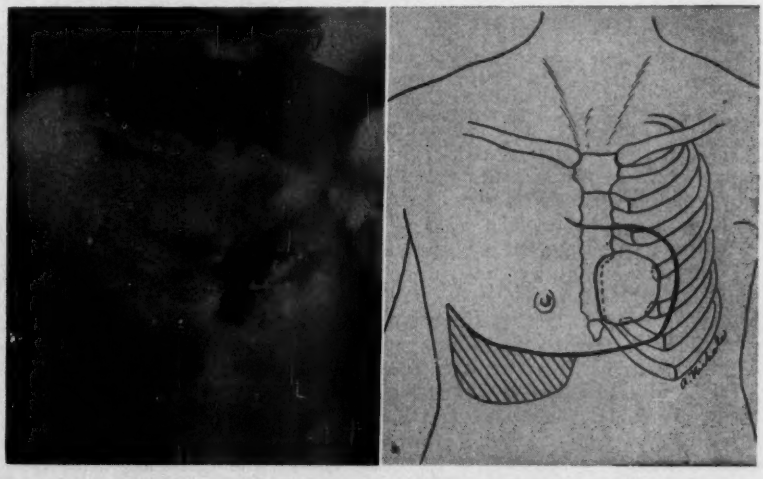

Fig. 3a. Photograph of patient in case 2 preoperatively.
b. Diagrammatic sketch showing defect and rotation of opposite breast for soft tissue coverage. The shaded area represents the donor area of the breast, covered by a split-thickness skin graft.

7.5 by 6 cm. full-thickness resection of the chest wall. Four costal cartilages and the left half of the sternum were included in the specimen which histologically contained squamous cell carcinoma. Closure was obtained by rotation of the right breast over the defect, a split-thickness skin graft being used to cover the donor area (fig. 3b). This patient was last seen in April, 1951, when a metastatic nodule was noted below the right scapula. No local recurrence was present.

Comment: Rotation of the breast to close properly situated small defects such as this has been described by Pickrell[10] and Maier.[11] With larger defects, the threat of chest wall instability demands the use of an additional supporting structure as is illustrated by the next case.

CASE 3. Three weeks before admission to the hospital, M. M., a 72 year old white female, struck her right chest against the back of a streetcar seat

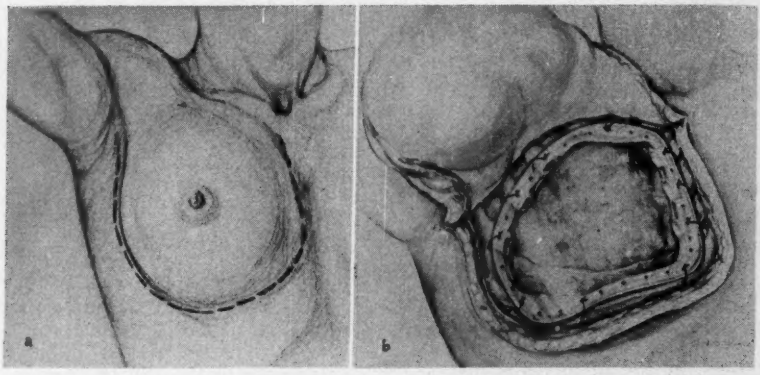

Fig. 4a. Sketches of surgical incision.
b. Surgical defect with Lucite plate attached to rib ends after removal of the tumor mass described in case 3.

when the vehicle was involved in a minor collision. The area of injury was painful and tender, but physical and roentgenologic examination at that time failed to reveal any serious abnormality. The patient was acutely conscious of the injured area and within a week by self-examination discovered that an ill-defined mass was present. Since her son (case 1) had died of a chest wall sarcoma one week previously, she quickly sought further medical attention. The presence of the ill-defined mass was confirmed and in addition by this time she had developed minimal lytic changes in the anterior end of her third rib. On March 1, 1946, her right breast was reflected upward and a radical resection of the chest wall with its attached soft tissues including the pectoral muscles was done (fig. 4a). The specimen included anterior segments of the second, third, and fourth ribs and histologically revealed a neurogenic sarcoma. The defect was closed with a preformed Lucite plate, 3/16 inch thick, which was anchored to the costal cartilages and residual rib ends with interrupted silk suture (fig. 4b). The breast was then sutured back in place for soft tissue coverage. The patient was never aware of this prosthesis and remained asymptomatic as far as the operative field was concerned. Unfortunately she died on Nov. 30, 1946, from widely disseminated metastases.

CASE 4. M. C., a 63 year old white male, first noticed a lump in his chest wall below the left clavicle in 1946. Prior to his admission to the University of Kansas Medical Center he had undergone two resections, each followed by recurrence of the tumor (fig. 5a). He had also received an indeterminate amount of roentgenotherapy. Physical examination of his chest anteriorly showed three subcutaneous nodules, each about 2 cm. in diameter, fixed to the chest wall in the left infraclavicular area. Roentgenologic studies failed to reveal pulmonary metastases or evidence of rib involvement. On July 16,

1949, he underwent a full-thickness resection of the upper left anterior chest wall. The specimen measured 17 by 8 by 4 cm. and included the anterior half of the left clavicle, segments of the first two ribs and attached costal cartilages together with part of the manubrium. Rhabdomyosarcoma was the final diagnosis. This defect was closed satisfactorily by upward mobilization of a bipedicled flap, a split-thickness skin graft being used to cover the donor area (fig. 5b). This patient's early postoperative course was uncomplicated, but he died in February 1950 as the result of extensive intrapulmonary spread of his disease.

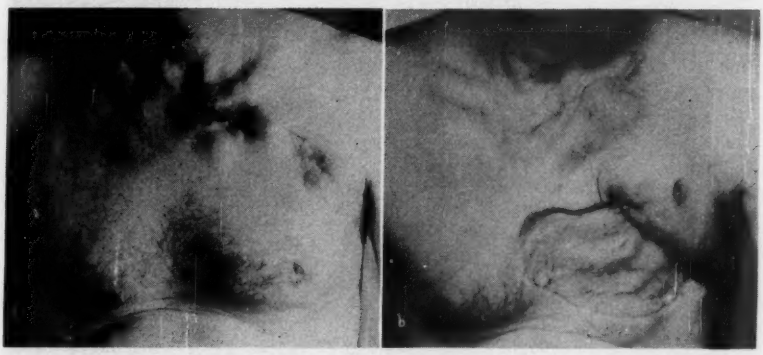

Fig. 5a. Photograph of patient discussed in case 4 with the rhabdomyosarcoma preoperatively.
b. The healed bipedicled flap postoperatively.

Comment: This illustrates well the soft tissue coverage of a large defect by utilizing a bipedicled flap.[12] Previous roentgenotherapy to this area made it necessary to excise sufficient tissue to preclude the possibility of necrosis due to an impaired blood supply. The actual bony defect was small enough so that chest wall stability was not a problem in this patient.

When excising malignancies of the chest wall a wide zone of normal tissue should be included in the resected specimen.[13] A full-thickness portion of the chest wall, including the pleura and usually an uninvolved rib on each side of the lesion, should be excised. Awareness of the magnitude of the residual defect by the surgeon should not compromise the extent of resection for malignancy.

CASE 5. P. C., a 47 year old white male, was admitted to the Medical Center on Jan. 11, 1949, with a history of sharp, constant pain localized in the right anterior part of his chest, occasionally radiating to the back. Since October 1948 he had noted the progressive enlargement of a mass which on physical examination was located over the anterior part of the right fifth rib. A roentgenologic examination in December 1948 was reported as revealing a rib fracture. However, by January 1949 physical examination showed a firm, fixed lump, 6 by 4 cm. overlying the right fifth costochondral junction. Roentgenograms at this time showed partial atelectasis of the middle lobe and a tumor mass involving the right fifth rib parasternally (fig. 6).

Thoracotomy was done on Feb. 5, 1949, with a full-thickness radical excision of the chest wall. The surgical specimen contained the anterior portions

of three ribs together with the intervening soft tissues and overlying skin, and histologically revealed anaplastic carcinoma. The residual defect measured 10 by 12 cm. While soft tissue coverage could have been accomplished by

Fig. 6a and b. Preoperative roentgenograms of patient in case 5 illustrating the tumor mass over the fifth rib anteriorly on the right and associated atelectasis of the middle lobe.

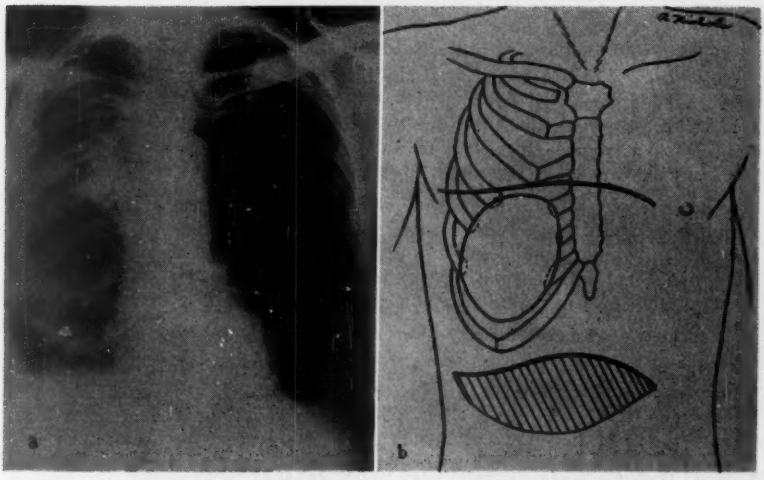

Fig. 7a. Postoperative roentgenogram of patient in case 5 showing the surgical defect and the radiolucency of the Lucite plate.
b. The sketch illustrates the soft tissue coverage by means of a bipedicled flap.

mobilizing a bipedicled flap from adjacent areas, the lack of subsequent stability would have been attended by paradoxical respiration and mediastinal mobility. Accordingly a Lucite plate was sutured to the adjacent rib ends with

interrupted steel wire sutures (fig. 7a) and then covered by a flap (fig. 7b). Postoperatively only one thoracentesis was necessary, this yielding 700 cc. of fluid on the sixth day. Unfortunately, generalized dissemination of the carcinoma occurred, and the patient died on March 27, 1949.

CASE 6. J. W., a 68 year old colored male entered the Medical Center on Jan. 11, 1949, complaining of a pain localized in the left side of his chest for two weeks. Roentgenograms revealed a large fusiform osteolytic tumor, 8 by

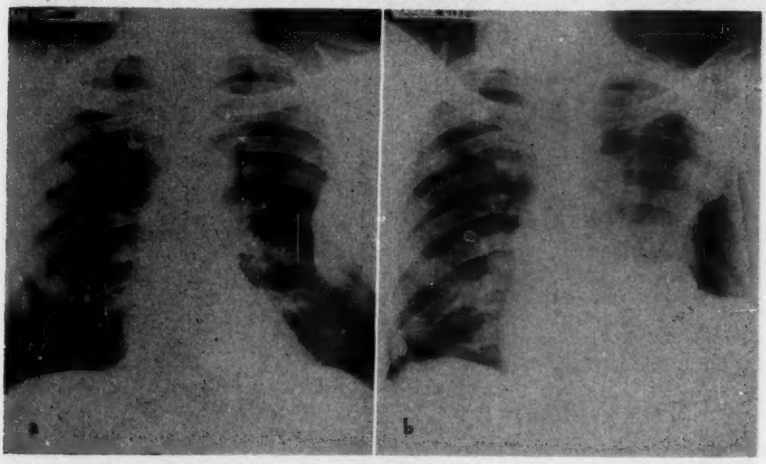

Fig. 8a. Preoperative roentgenogram of patient in case 6 illustrating location and size of tumor, its intrapleural extension, and the surgical defect covered by Lucite plate, sutured with stainless steel wire.
b. Postoperative roentgenogram of same patient.

10 cm., involving the left fifth rib in its mid axillary portion, and extending into the pleural cavity (fig. 8a). Further roentgenologic examinations, including an intravenous pyelogram, were interpreted as normal. Thoracotomy was performed on Jan. 19, 1949, with excision of segments of three ribs, centered about the tumor, and attached soft tissues. The surgical specimen measured 6 by 10 by 12 cm., histologic examination revealing hypernephroma. A previously prepared Lucite plate was inserted into the defect and sutured to adjacent rib ends with stainless steel wire (fig. 8b). Since this tumor was contained completely within the periosteum, overlying soft tissues were not excised and could be used for coverage of the prosthesis. Postoperatively 500 cc. of fluid was removed by thoracentesis on the sixth day. This patient was referred to the urological service for treatment of his primary tumor, but failed to return for further care.

Comment: This case illustrates the occasional instance when a prosthesis may be necessary for stability of the chest wall without requiring the construction of a flap or shifting of tissues for soft part coverage.

CASE 7. W. A., a 64 year old white male, was admitted on April 8, 1950. He related a history of definite soreness limited to the left side of the chest and accompanied by hemoptysis for one month. Roentgenogram of the chest showed an osteolytic mass 5 by 10 cm. involving the left third rib in its pos-

terolateral position and protruding into the pleural cavity (fig. 9). Thoracotomy was done on April 12, 1950. A large tumor mass arising in the left upper lobe and invading the posterior chest wall was found. The left upper lobe in continuity with a portion of the chest wall containing segments of the second, third, fourth, and fifth ribs was resected. The histologic diagnosis was squamous cell carcinoma of the upper lobe with invasion of the chest wall. The scapula was allowed to collapse into the residual defect thus providing

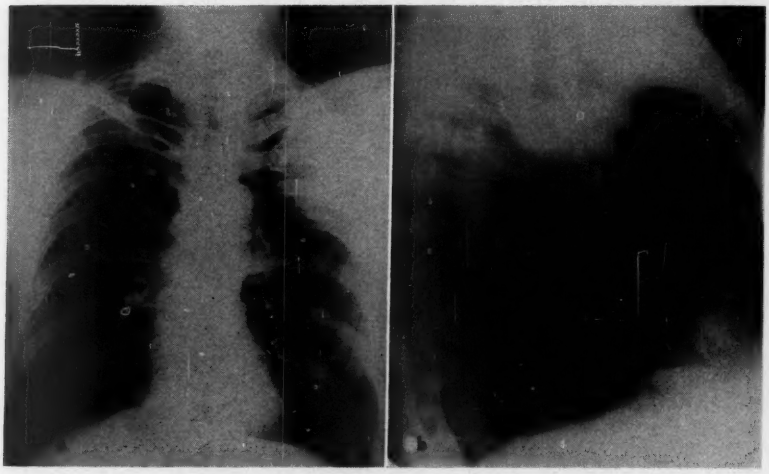

Fig. 9a and b. Preoperative roentgenograms of patient in case 7 depicting squamous cell carcinoma of the left upper lobe extending into the parietal pleura and chest wall.

stable coverage. Two thoracenteses were done postoperatively on the seventh and tenth days obtaining a total of 1650 cc. of fluid. The patient was last seen on Nov. 17, 1950, with no evidence of recurrence.

Comment: The problem of paradoxical respiration and undue mediastinal mobility is not usually encountered in resections of the posterior part of the chest wall. The remaining rib segments anteriorly together with the overlying musculature and bony substance of the scapula provide a good covering for resections in this area. The possibility of cure was enhanced by the extensive resection in continuity.

CASE 8. T. D., a 31 year old white male, was run over by an automobile when he was 8 years old, probably sustaining an undiagnosed diaphragmatic hernia. For the next two years he had postprandial cramping and abdominal pain. An incidental army roentgenogram in 1941 was reported as showing diaphragmatic eventration, but nevertheless he was accepted for military service. He remained asymptomatic until January, 1948, when he fell, striking his left side and experiencing severe pain with dyspnea. Barium swallow revealed the stomach and colon to be in his left pleural cavity (fig. 10a).

On Feb. 16, 1948, he was admitted to the Veterans' Administration Hospital at Wadsworth, Kansas, where a thoracotomy was performed. The small intestine, stomach, and colon were replaced into the abdominal cavity and the

ruptured edges of the diaphragm sutured together with continuous sutures of chromic catgut. Five months later the diaphragmatic hernia recurred. Because it was believed that there was insufficient tissue to effect a secure closure, the insertion of a Lucite plate was advised. Thoracotomy was done on July 12, 1948, and a 10 by 10 cm. defect in the dome of the diaphragm was closed, utilizing a 3/16 inch Lucite plate fastened with braided silk sutures. Five thoracenteses during an otherwise uneventful two weeks postoperative course yielded a total of 1800 cc. of serosanguineous fluid. His subsequent course has been uneventful during the past three and a half years (fig. 10b).

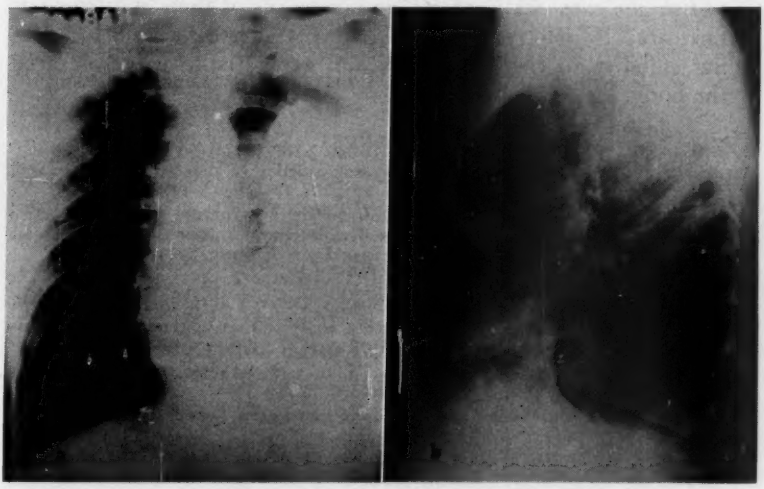

Fig. 10a. Roentgenogram of patient described in case 8 illustrating the diaphragmatic hernia in 1948 before repair.

b. The Lucite plate is noted as well as the absence of pleural reaction or exudate (1951).

Comment: A plastic prosthesis was admirably suited to the repair of this recurrent diaphragmatic hernia, for it allowed the closure of an extensive diaphragmatic defect without necessitating lung collapse. To have controlled this situation by thoracoplasty would have resulted in marked ventilatory impairment. The lack of any symptoms or signs of localized difficulty attests to the tissue tolerance of Lucite and its applicability in such an instance.

SUMMARY

Reconstructive methods for defects of the chest wall involve the fundamental problems of primary wound closure and the maintenance of stability, the latter depending upon the location and the magnitude of the defect. The use of bone and periosteal flaps, and of fascia lata strips appear to be limited to small defects. Thoracoplasty, with its collapse of the chest wall, imposes the serious consequence of decreased ventilatory function.

In large defects stability of the chest wall must be secured to prevent the deleterious effects of paradoxical respiration and abnormal mediastinal mobility, and to permit, particularly in the immediate postoperative period, the effect of a forceful cough. External appliances have generally proved unsatisfactory. Metal prostheses seriously limit roentgenologic examination of the underlying lung parenchyma.

The practicability of preformed Lucite plates for the reconstruction of major chest wall defects, and instances of their employment, is illustrated by selected cases. Lucite plates are suitable for providing stability to the chest wall, and are satisfactorily tolerated by the body.

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MALIGNANCY OF THE EXTERNAL EAR

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Carcinoma arising on the external ear gives the physician the advantage of observation, detection, and a chance of cure rarely present in dealing with malignancies occurring in other areas of the body. In spite of such obviousness, deaths still result from neglect, inadequate management, or the rare uncontrollable highly malignant lesion.

Epithelioma of the skin usually spreads locally by direct infiltration of contiguous tissue from skin cancer of the pinna or external auditory meatus. Metastases to the regional preauricular, submaxillary, and cervical lymph nodes are infrequent. Not more than 5 per cent of all epidermoid carcinomas of the face and neck metastasize.[1] However, the disappointing results of inadequate treatment and recurrences have led us to reiterate salient well established methods of treatment. The all too frequent necessity of mutilation by surgery late in the course of the disease bespeaks of inadequate early treatment.

New growths and chronic discharges from the ear canal should be considered malignant until proved otherwise. Prompt biopsy specimens should be taken before treatment is instituted. A knowledge of the histopathologic type of tumor and its degree of malignancy will direct a proper approach to the disease. Prognosis closely parallels Broders' grading of malignancy.[2] The rate of cure reported by Mohs[3] was 91 per cent for epidermoid skin lesions of grades I and II, but dropped to 60 per cent and 25 per cent for lesions of grades III and IV. The reason for a drop in the cure rate is the greater tendency toward metastases in the higher grade of malignancy. The location of the lesion also influences the prognosis. Carcinomas more deeply situated in the ear are closer to vital inaccessible areas, rendering eradication and removal less likely.[4]

Skillful and adequate treatment of epidermoid carcinoma of the ear has produced creditable cure rates. Various series dealing with three to five year arrests for basal cell carcinoma are quoted to be from 93 per cent to 96 per cent. Squamous cell carcinoma is reported as arrested in from 77 per cent to 80 per cent of the cases.[5,6,7]

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Early lesions can be treated adequately by either roentgenotherapy, radium ray therapy or surgery. The amount of roentgenotherapy or radium ray therapy given should be determined and administered by well trained roentgenologists. Fixation of the tumor to the auricular cartilage requires a wide full thickness removal of the involved segment of ear. When bone is involved, the outer table of the skull must be surgically removed.

Surgical removal offers many advantages. Sharp surgical excision of the tumor gives the pathologist an opportunity to study the sections and to determine if the excision has been wide enough. A large defect of the skin of the ear or adjacent scalp can be easily closed with a split thickness skin graft. Direct local flaps, usually postauricular, can be used to cover exposed bone or replace a full thickness loss of the ear. Primary healing may take place with a minimum of deformity. The use of cautery destruction of a previously untreated lesion has definite disadvantages since no specimen is available for study, and healing is usually delayed and occurs by scar tissue contracture.

The surgical approach to carcinoma of the ear calls for a wide excision of the tumor. The limits of removal should include an apparently normal zone of tissue .5 to 1.0 cm. beyond the visible or palpable extent of the lesion. In depth the excision must be carried well below the tumor. Mohs[3] has shown the invasiveness of epitheliomas by microscopically controlled excision. Tumor cells spread along the interstices of normal tissue often far beyond the expected limits. Radicalism, in the sense of insuring a complete removal of the cancer, should be employed early, not late, in the disease. Compromise of the principles of radical adequacy usually made because of surgical timidity or for cosmetic reasons often spells doom for the patient. Preservation of the facial nerve should not be considered in these radical extirpations for cancer. The best chance for arrest lies in early detection and complete removal.

Prophylactic neck dissections for carcinoma of the pinna or external ear canal are not recommended because of the low incidence of metastases. Repeated follow-up observation is relied upon to pick up any secondary lymph node spread. Radical en bloc removal of the involved nodes is then done if nodes are suspected of bearing metastases. Basal cell carcinoma has the well-known tendency to become deeply invasive and resistant to treatment. When metastases occur, squamous cell elements are present with those of basal cell types.[8,9] Large ulcerated lesions, perichondritis, and recurrences after inadequate surgery or roentgenotherapy usually require extensive destructive surgery. Wide surgical excision followed by actual cautery to the base of the wound is advised. Postoperative roent-

genotherapy to areas such as the external auditory meatus is often given when surgery would be inadequate or dangerous. Because of the tendency for recurrence even after extensive surgery, cautery and roentgenotherapy, we prefer to leave these wounds open. The salvage rate of recurrent carcinoma in Mohs'[3] hands was 53 per cent as compared to 91 per cent for patients who had had no previous treatment.

Definitive closure of areas of wide destruction in recurrent carcinoma should be deferred until the lesion is controlled. A thin skin graft, however, is useful to convert a wide open draining wound into a closed clean one. Repeated frequent observations of the patient will suffice for a check-up and the presence of the grafts will not inhibit the detection of recurrence.

The following case reports are examples of difficult problems with advanced disease and demonstrate that the outcome is not always favorable.

CASE 1. D. K., a 73 year old male, was admitted on May 8, 1949. Previous excision in the concha had been done in 1948 but the wound never healed. Biopsy specimen on admission revealed a squamous cell epithelioma, grade II. A preauricular ulcerating lesion 4 by 3 cm. was present extending onto the face and invading the ear and external auditory meatus (fig. 1-A). No re-

Fig. 1a. Ulcerating squamous cell carcinoma (4 by 3 cm.) extending locally into the ear and skin of the face.

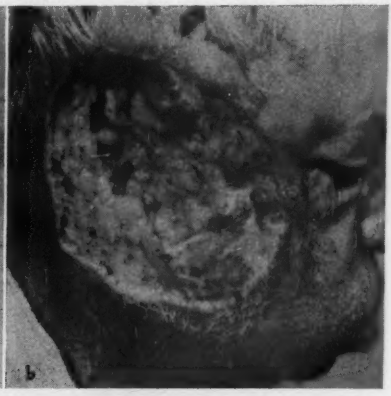

Fig. 1b. Extent of radical cautery excision (8 by 8 cm.). The seventh nerve has also been destroyed.

gional adenopathy was present. On May 12, a radical excision 8 by 8 cm. was done (fig. 1-b). The tumor was invading the buccinator and temporalis muscle, ear, and external auditory meatus. Electrocautery was applied to the surgical field. The external auditory meatus and ear canal were treated with 2156 roentgens. On July 10, 1950, recurrence was noted inferior to the auditory canal. This was removed by cautery excision. No recurrence was noted on the date of the last follow-up on Jan. 4, 1951.

CASE 2. G. S., a 68 year old white male, was admitted on July 17, 1946. He had a history of a 10 year old lesion progressively increasing in size. The original lesion began behind the ear over the mastoid area. Roentgenotherapy, 1430 roentgens, had been given one year prior to admission. On admission the recurrent cancer had destroyed the ear except for a part of the lobe. An ulcerated crater measuring 6 by 8 cm. was present. A biopsy specimen showed squamous cell carcinoma, Broders' type II. On July 29, cautery excision was performed. Two weeks later the upper one-half of the wound was closed with a split graft. On September 5, the outer necrotic table of the temporal and mastoid bones were removed; the area was allowed to granulate, to be covered later with a split graft. There was no evidence of recurrence of the original carcinoma when the area was grafted. Areas of dermatitis and hyperkeratosis have been carefully watched. On Feb. 15, 1951, high on the temporal area above the resected field, a small basal cell carcinoma was excised and the defect closed with a split skin graft. Good coverage was obtained.

Comment: The slow course of his disease makes his outlook favorable, providing he returns faithfully for his follow-up visits and has definitely new sites of origin treated in time.

CASE 3. R. I., a 48 year old white female, was admitted on Jan. 11, 1950. A progressively destructive lesion of the pinna had been present for five years (fig. 2-a). Repeated treatments with ultraviolet rays had not altered the progress of the growth. A biopsy specimen revealed basal cell epithelioma. The lower one-half of the external ear was destroyed and the tumor (4 by 2

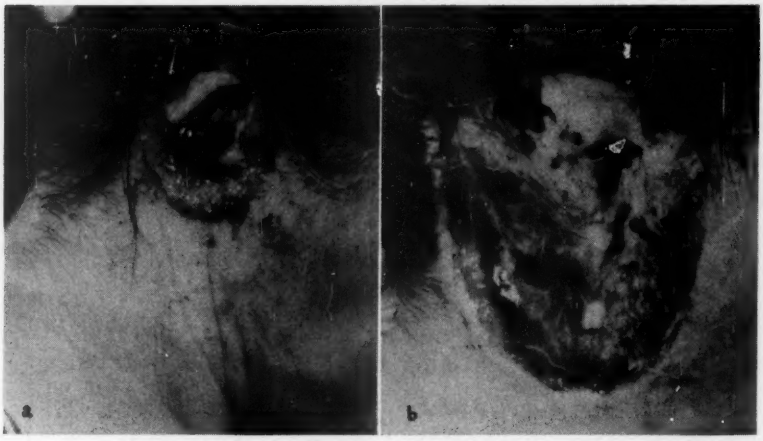

Fig. 2a. Destructive and ulcerative basal cell carcinoma extending into the auditory canal.

Fig. 2b. Wide cautery excision (9 by 11 cm.) destroying also the outer table of the mastoid and temporal bone. Postoperative roentgenotherapy was given to the external auditory meatus area.

cm.) was invading the external auditory canal for a distance of 1 cm. No palpable regional adenopathy was present. On Jan. 16, a wide excision (9 by 11 cm.) denuded the upper temporal bone and mastoid area and the entire field was cauterized with the Bovie unit. The external auditory canal was

curetted for a distance of 2 cm. in depth. The wound was left open for observation (fig. 2-b). Postoperatively the ear canal was treated with a total dose of 3440 roentgens. On Jan. 5, 1951, a sequestrectomy of the necrotic outer tables of the temporal and mastoid bones was done. On Jan. 11, a split graft was applied to the granulating area. There has been no evidence of recurrence when last seen in September 1951 (fig. 2-c).

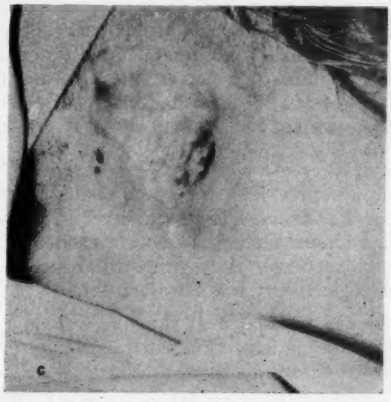

Fig. 2c. Sequestrectomy of necrotic bone and coverage with split skin graft one year after original surgery.

Comment: Knowing the resistant and deeply invasive character of basal cell carcinoma, a radical excision was done. Deliberate sacrifice of the ear and seventh nerve was accepted to insure removal of the tumor. The surgical wound was left open for observation and control of any recurrence. Actual cauterization was employed to destroy the outer table of adjacent bone. This type deformity is less obvious in the female with long hair to hide the defect.

CASE 4. C. C. Y., a 54 year old white male, was admitted on Jan. 29, 1950. He first noticed a small nodule on the left superior helix rim in 1944. He was treated symptomatically with topical penicillin and ultraviolet light. The lesion began to enlarge slowly. In 1947 this lesion was treated with cautery and radium rays. In 1949, when the first biopsy specimen revealed squamous cell carcinoma of a low grade malignancy, surgical removal and split skin graft coverage was done. In October 1949 swelling over the temporomandibular joint developed with a chronic drainage from the ear. He was treated for three months with penicillin and sulfa powder. On admission, roentgenologic examination of the skull was negative. Preauricular lymph nodes were palpably large and indurated, but no palpable nodes were present in the neck. A biopsy specimen on Jan. 30, 1950, revealed anaplastic carcinoma. On Jan. 31, 1950, a radical surgical removal of the area was done. The condylar head and neck were resected with the posterior half of the zygomatic arch, the lining of the glenoid cavity, some temporal bone, and posterior portion of the parotid gland. The entire operative field was meticulously heavily electrocauterized. Postoperative roentgenotherapy was given, 3450 roentgens, to the area corresponding to the ear canal and 1888 roentgens to the lower limit of the excised field. One month later 4200 roentgens was given to the periphery of the defect. Five months later recurrence was noted over the ramus of the

mandible and infiltrating the pterygoid muscles and base of the brain. On July 10, 2500 mg. hours of radium was given. One month later, the internal maxillary and the lingual arteries required ligation to control severe hemorrhage. The patient died two months later.

Comment: The opportunity for a cure was missed by a failure to render early adequate treatment. The small original size and location of this epidermoid carcinoma would make the chances of early removal and cure seem likely. Here we see the mutation of a low grade carcinoma to a highly malignant one due to repeated stimuli and inadequate treatment. Recurrent carcinomas after insufficient amounts of radiation are very resistant to any form of treatment. Prompt recognition of metastatic nodes and their early removal increase the likelihood of salvage, providing the primary lesion is arrested.

CASE 5. R. C., a 66 year old white male, was seen on May 5, 1951. For several weeks he had noticed a small red raised nodule in the concha just posterior to the meatus. The lesion measured 5 mm. in diameter. Under local anesthesia the tumor and surrounding skin were excised for a distance of 1.7 by 1.3 cm. down to the cartilage. A free full thickness skin graft was used to fill the defect. Pathologic report was fibrosarcoma.

These early lesions can be excised as this one was on an outpatient basis, minimizing expense to the patient. The early adequate excision with immediate coverage to obviate deformity is an ideal method of treating early malignancies.

SUMMARY

Early recognition, biopsy specimens, and the proper application of treatment will lead to a greater salvage rate. Injudicious application of any one method can lead to failure and render incurable a lesion which might have been arrested. Close follow-up and observation to detect recurrence or metastases is the responsibility of the physician treating the patient.

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DAILY MUCIN SECRETION IN NORMAL AND VAGOTOMIZED TOTAL GASTRIC POUCHES OF DOGS

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The significance of mucus in gastric secretion, the mucigogues, and the physiology of mucus in normal and diseased states have been neglected and controversial subjects for many years. In 1800 Glover[1] mentioned that the mucus probably acted as a protective mechanism for the gastric mucosa and this was subsequently reiterated by Beaumont,[2] Bernard,[3] Heidenhain,[4] and others.[5-8] Kaufmann[9] formulated the term "gastric amyxorrhea" to apply to those patients whom he thought had a deficiency of mucus production.

Numerous investigators, analyzing mucus and its secretion to stimuli, reported differences, both qualitative and quantitative, between normal individuals and those with gastroduodenal disturbances.[10-13] As a result of these findings, several advised the administration of commercially prepared mucin to ulcer patients to augment a postulated deficiency of this substance.[14-18] Others, however, have failed to elicit any appreciable difference in mucin production between the same groups.[19-25]

Many of these apparently contradictory clinical results can be resolved when it is appreciated that only recently, after the careful work of Glass and his associates,[26-29] has it been possible to recognize and determine accurately the various mucin fractions in gastric juice.

Although several biochemical and physiological investigations have been made of mucin, only a few conclusions are universally accepted. Briefly, these are:

Mucin found in the stomach occurs in two grossly different forms:[30]

(a) that noted as shreds and lumps in the gastric juice. This forms a thick, viscous protective covering for the gastric mucosa and is generally called the visible surface epithelial mucus, and

(b) that portion dissolved in the gastric juice. This is a heterogeneous mixture of at least two chemically different compounds. One of these, the dissolved mucoproteose, is the dissolution and degradation product of the surface epithelial mucus. The other,

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the dissolved mucoprotein,[31-32] is the secretion of the mucus cells of the gastric glands.

The exact chemical composition of each of these various components has not been ascertained, but each has the basic structure of a polymerized molecule of globulin with an attached polysaccharide. In addition, the dissolved mucoproteose contains uronic acid and the dissolved mucoprotein, hexosamine.[33] In general, mucin has a high calcium content and variable amounts of chloride, bicarbonate, and phosphate. Its pH averages 7.0, but may be as high as 9.0. Such high values reflect the loss of carbon dioxide from the native secretion between the times of its formation and measurement.[34-36] Other properties imparting to mucin its specialized function are adhesiveness,[37] cohesiveness,[8,38] viscosity,[38,39] adsorptive power,[38,40-42] and acid-neutralizing ability.[34,38,43] Hollander[44] has stressed these various features as protective mechanisms for the gastric mucosa, emphasizing particularly the viscosity of the surface epithelial mucus and the acid-neutralizing ability of the dissolved fractions.

Experiments with dogs have demonstrated that sham feeding caused a pronounced increase in dissolved mucin secretion. No correlation was found between the mucin response and either acid or the pepsin production.[45] Secretion of mucin may be greatly augmented by mechanical or chemical irritants acting locally on the gastric mucosa.[35,46] Both vagal and splanchnic stimulation result in an increased production of mucin, each probably affecting a different area of the stomach or a different cell type.[47-50] Histophysiologic studies do not support the hypothesis that mucin secretion is secondary to motor activity of the stomach.[51]

Secretion of the dissolved mucoprotein has been demonstrated to be dependent upon vagal innervation and indeed the increase of this fraction to the stimulus of insulin-hypoglycemia has been claimed to be a more reliable test of vagal integrity than the acid increase.[52-54]

Our previous studies in secretions collected from total gastric pouches of dogs[55] stimulated us to study their daily output of the various mucin fractions. The available literature contains no reference regarding the total amount of mucin secreted by the stomach in 24 hours.

Method. Total isolated gastric pouches were constructed in two groups of mongrel dogs by the method originally credited to Fremont[56] and subsequently used by Dragstedt[57] and others[58] for the study of gastric secretion. Gastrointestinal continuity was reestablished by either an end to end or an end to side esophagoduodenostomy, the secretion from the isolated stomach being drained to the outside through a stainless steel cannula. Prior to surgery, the

TABLE I

Summary of Average Daily Gastric Secretion from Total Gastric Pouches in Dogs

DOG	Ml. per day	pH	Free Acid mEq.	Total Acid mEq.	Visible Mucus ml.	Mucoid of Visible Mucus mg. %	Total Mucoid in Sample mg.*	Dissolved Mucin ml.	Mucoproteose mg. %	Total Mucoproteose in Sample mg.*	Mucoprotein mg. %	Total Mucoprotein in Sample mg.*
Intact Pouches												
# 38	324	1.8	8.5	14.4	20	2125	417	304	229	729	91	302
44	385	1.4	33.9	47.5	14			371	94	316	160	567
51	156	1.6	9.0	12.2	14	2593	362	142	336	404	276	358
55	516	1.6	37.1	56.3	29	5299	1224	485	138	705	106	582
56	335	1.9	28.3	41.7	27			297	103	216	69	141
58	317	1.4	19.9	25.9	18	3553	662	299	77	228	77	230
59	373	1.4	33.4	42.3	18	4105	645	349	165	551	133	457
Average	344	1.6	24.3	34.3	20	3535	662	321	163	450	130	377
Vagotomized Pouches												
# 27	177	1.6	8.1	12.4	38	1572	540	139	365	440		
28	91	2.0	3.7	5.5	3	2135	63	88	505	424	44	36
29	174	1.6	9.6	14.2	5	3055	165	169	396	627		
39	244	1.7	16.5	20.0	22	1961	413	222	138	223	88	142
102	119	1.6	18.8	22.9	10	2542	246	109	174	179	62	81
125	201	1.4	7.0	8.8	8	3796	304	193	125	204	43	64
Average	168	1.7	10.6	14.0	14	2510	289	153	284	350	59	81

*Total amount in sample equals concentration times volume.

dogs were given vermifuges, maintained on a high protein diet, and acclimated to the kennels for at least four weeks. In one group (7 animals) all nerves to the pouch were allowed to remain intact, while in the other (6 animals) complete vagotomy at the level of the cardia was done. Twenty-four hour collections of gastric juice were obtained by connecting to the cannula a rubber bladder, this being supported by a lightweight canvas bag held by straps across the back of the animal. Collections were made for periods varying from two weeks to two months.

The gastric samples were measured for total volume, analyzed for pH by the glass electrode method, and titrated with 0.1 normal sodium hydroxide using Topfer's and phenolphthalein reagents for milliequivalents of free and total acidity. The visible mucus and its mucoid, and the dissolved mucoproteose and the dissolved mucoprotein were determined after the method described by Glass.[28] This is based on first centrifuging visible mucus from the gastric juice. The two fractions in the dissolved mucin are then chemically separated and each portion is quantitatively estimated on the basis of its tyrosine content, utilizing the Folin-Ciocalteau[59] colorimetric reaction.

The results are presented in table I.

Discussion

A consideration of the experimental data reveals that the values obtained for daily volumes, pH readings, and milliequivalents of free and total acidity are within the ranges found by others in daily secretion from intact and vagotomized total canine gastric pouches.

The volume of visible mucus in the vagotomized pouches (14 ml.) is less than the mean volume in normal pouches (20 ml.), although considerable variation is present in the individual animals of the vagotomized group. The mucoid of the visible mucus is less in the vagotomized animals, both with respect to concentration and total secretion.

The dissolved mucoproteose concentration average is greater in the pouches subjected to vagotomy, a finding previously noted in humans after vagotomy.[54] However, the total amount secreted is less in the vagotomy group, a reflection of the marked decrease in the gastric volume following this procedure.

Both the concentration and the total quantities of the dissolved mucoprotein are substantially less in the vagotomized, as compared with the intact pouches. This further illustrates the dependence of the secretion of this fraction on vagal impulses as has been previously commented upon by numerous authors.[52-54]

Because of the reduced total quantities of visible mucus and mucoid, with their physical features of high viscosity, and the reduced quantities of the dissolved mucin fractions, with their chemical acid-neutralizing ability, the vagotomized gastric mucosa presents an increased susceptibility towards ulceration as compared to the normal stomach.

SUMMARY

1. Studies were made of 24 hour collections of gastric juice from total pouches in 7 normal dogs and 6 subjected to vagotomy with particular reference to mucin analysis.

2. Analyses of the gastric juice samples revealed a decrease in the visible mucus and mucoid fractions in the vagotomized group. This is the fraction of mucin affording surface coverage protection to the mucosa.

3. The concentration of dissolved mucoproteose was increased in pouches that had been vagotomized but the total amount was decreased.

4. Both the concentration and the quantity of the dissolved mucoprotein was markedly less in the vagotomized animals.

5. The factors in a vagotomized stomach of a decreased quantity of visible mucus and mucoid combined with a decreased quantity of the dissolved fractions, particularly the mucoprotein, reduce both the physical and chemical qualities normally protecting the mucosa of the gastric wall.

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METABOLISM OF PROCAINE FOLLOWING ITS SUBARACHNOID INJECTION*

A Preliminary Report

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SPINAL anesthesia has been in general clinical use for almost half a century, but knowledge of the mechanism producing the anesthesia is far from complete. The early work of Smith and Porter,[1] showing a large quantity of procaine remaining in the spinal fluid as long as 25 minutes after injection, has not been confirmed by other investigators.[2,3,4] Goldberg et al.[5] found 10 per cent of the injected procaine remaining in the spinal fluid when anesthesia was just beginning to wear off. Most investigators have found procaine removed from the spinal fluid more rapidly than this observation would suggest.

No appreciable hydrolysis of procaine by spinal fluid occurs in vitro, despite an early report to the contrary by Thompson.[6]

The work of Wallace and Brodie,[7] Burford,[8] and others[9] has demonstrated that the most probable route for the absorption of spinal fluid, and substances dissolved in it, is via the perivascular spaces, and, to a lesser degree, by the spinal arachnoid villi demonstrated by Elman.[10] More recent studies by Howarth and Cooper[11] confirm these observations. These workers, using radioactive isotopes, found that in no case, after lumbar injection of dibromprocaine, was a concentration found in the cisternal cerebrospinal fluid sufficient to account for the rapid fall in concentration in the lumbar region.

Once it reaches the blood, procaine is hydrolyzed by an esterase present in plasma to para-aminobenzoic acid and diethylaminoethanol. This procaine esterase is probably formed by the liver.[12] According to the previously cited work of Goldberg et al., nearly all of the injected procaine can be recovered from the urine as its detoxification products. They found about equal parts of para-acetoaminobenzoic acid, para-acetoaminchippuric acid, and para-acetoaminobenzoyl glycuronate. In their opinion, if any procaine is "fixed" by nerve tissue, the amount must be very small.

Rapp[13] has reported that procaine inhibits the reaction between acetylcholine and creatine phosphate in nerve extracts. Since this

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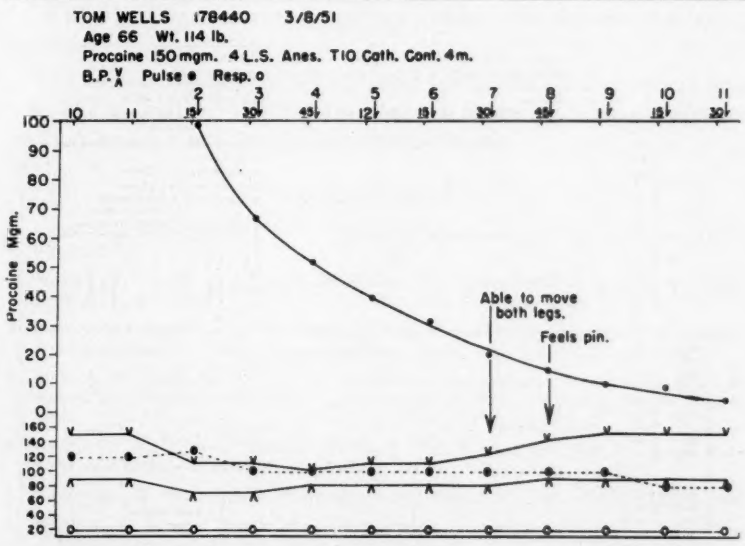
TABLE 1

Pt.	*Age*	*Procedure*	*Operative Time*	*Procaine (Total Dose)*	*Level Anes.*
ET	66	Transurethral resection	3 hr. 37 min.	150 mg.	T10
TW	66	Transurethral resection	1 hr. 28 min.	150 mg.	T10
JM	54	Total cystectomy. Rt. cutaneous ureterostomy	4 hr. 29 min.	375 mg.	T 7
SH	55	Rt. Nephrostomy	3 hr. 15 min.	300 mg.	T 4
MS	70	Ventral Herniorrhaphy	5 hr. 25 min.	275 mg.	T 4

reaction has been proposed as a part of the mechanism associated with propagation of the nerve impulse by Nachmansohn et al.,[14] any elucidation of the point might be of basic importance. Studies concerning the "fixation," if any, of procaine by nerve tissue are in progress in our department. The following is a preliminary report of 5 cases.

Chart 1


TOM WELLS 178440 3/8/51
Age 66 Wt. 114 lb.
Procaine 150 mgm. 4 L.S. Anes. T10 Cath. Cont. 4m.
B.P. Pulse Resp.
Procaine Mgm.
Able to move both legs.
Feels pin.

METHOD

Continuous subarachnoid anesthesia with procaine hydrochloride, 2.5 per cent in Ringer's Solution (catheter technic) was administered to 5 patients for various surgical procedures, as shown in table 1. Samples of spinal fluid were withdrawn at intervals follow-

Chart 2

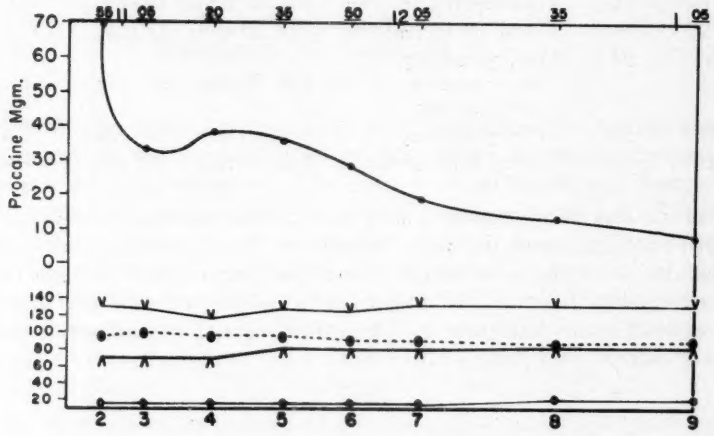
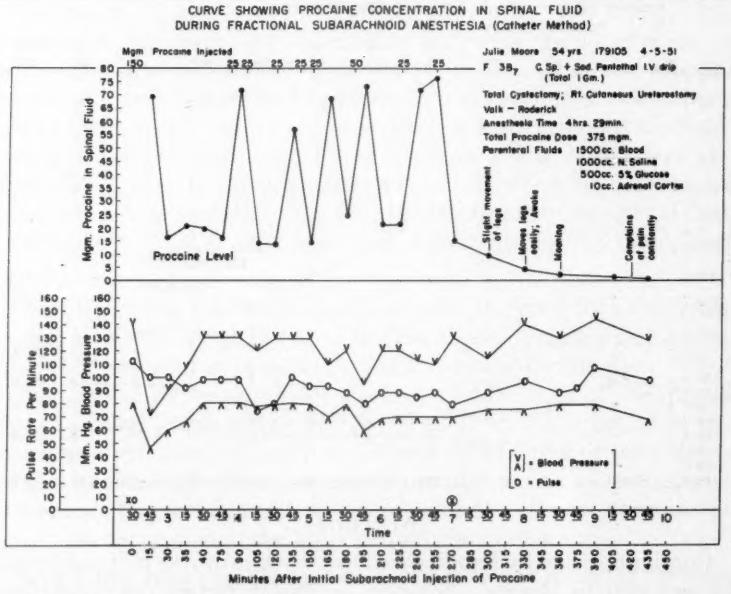


Chart 3


CURVE SHOWING PROCAINE CONCENTRATION IN SPINAL FLUID
DURING FRACTIONAL SUBARACHNOID ANESTHESIA (Catheter Method)
Mgm Procaine Injected
Julie Moore 54 yrs. 179105 4-5-51
Mgm. Procaine in Spinal Fluid
Procaine Level
Pulse Rate Per Minute
Mm. Hg. Blood Pressure
Time
Minutes After Initial Subarachnoid Injection of Procaine

ing induction, and were analyzed for concentrations of procaine and para-aminobenzoic acid according to the method of Bratton and

Marshall, as modified by Kuang et al.[15] The Tuohy spinal catheter was left in situ while these patients were in the postoperative recovery room, so that the concentrations could be followed until sensory functions returned. Studies of selected cases are shown in Charts 1, 2, and 3.

Discussion

These studies demonstrate the rapid initial fall and subsequent slowly decreasing concentration reported by previous workers. It appears probable, as postulated by Koster, Shapiro and Leikensohn, that the initial fall is due to spread of the anesthetic with consequent dilution, while the secondary fall is due to local utilization or destruction. The lowest concentrations at which sensory anesthesia was still present ranged from 5 to 15 mg. per hundred milliliters. This finding is in agreement with results reported by Helrich and his associates.[4]

Summary

Preliminary studies of the concentration of procaine in spinal fluid of 5 patients during continuous subarachnoid anesthesia are reported.

The lowest concentrations of procaine in the lumbar spinal fluid sufficient to maintain sensory anesthesia were found to range between 5 and 15 mg. per hundred milliliters.

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FEVER IN MALIGNANT DISEASE*

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FEVER as a symptom of malignant disease has long been recognized and was especially emphasized in the literature at the turn of the century. Frequent mention has been made of fever in malignant abdominal neoplasms in the 1880s and 1890s, but in recent years these observations have receded into the background to be overshadowed, like many other clinical observations, by purely laboratory findings.

In reviewing the literature for discussions of fever and its relation to malignant neoplasm, contributions are rare in recent years and frequent prior to 30 years ago. The most comprehensive article is a report by Freudweiler[1] from the Zurich Clinic embracing 475 patients with carcinoma as the basis of fever. Over half of these patients had carcinomas of the stomach and all but 40 had gastrointestinal cancers. Hyperpyrexia occurred in 25 per cent of pharyngeal and esophageal cancers. Osler and McCrae[2] reported 150 cases of gastric carcinoma with fever occurring in 40 per cent and Friedenwald[3] found 43 per cent of patients with fever in a similar series of stomach cancers. Smithies and Ochsner[4] observed that one-third of the patients with gastric cancer have elevated temperatures during some part of their disease. Musser[5,6,7] states that 18 per cent of those with carcinomas of the biliary tree had fever.

Pedrini[8] makes the statement that two types of neoplastic fever should be distinguished, one due entirely to the growth and the other representing a complication of the disease. He believed that cancers of the pleura and liver were more apt to be associated with fever than other organs. Primary cancer of the liver produced fever in 100 per cent of the cases of Cabot.[9] He also stated that, in his experience, 80 per cent of patients with primary localized pancreatic carcinomas and 71 per cent of patients with prostatic cancer had fever. The first reported case of fever in hypernephroma was made by Israel[10] in 1896. He later reported that 18.3 per cent of kidney cancers produce fever. Carcinoma of the adrenal cortex is nearly always accompanied by fever (Puig).[11]

The significance of fever of varying types accompanying cancer has been noted mostly in the German literature and these authors particularly stress the intermittent variety. Wunderlich[12] seems to have made the earliest observation that fever may be intermittent in character and in such instances the course of the disease was apt

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to be rapid. Liebert[13] describes a "light and hectic" fever of carcinomatosis. Hampein and Riga[14,15] have pointed out that a high septic intermittent fever with chills and sweats lasting over a long period and simulating malaria is produced by carcinoma. His observation predates the reports of Pel and Ebstein[16] by two years when the latter authors proposed the Pel-Ebstein "Ruckfallsfieber."

Freudweiler divides his material into four classes according to fever type. Six per cent of his patients with carcinoma had a continuous fever with a diurnal variation of less than one degree. Fourteen and one-half per cent of the patients had malaria-like paroxysms often accompanied by chills and recurring at regular intervals. Much more common were the occasional rises lasting no longer than three days and recurring at irregular intervals. Thirty-eight and one-half per cent of the patients fell in this group. A remittent or intermittent fever was the most common and was present in 41 per cent of his patients.

Briggs[17,18] studied 238 cases of cancer, 38 per cent of which had fever. Great care was taken to include only those cases of uncomplicated cancer that had no other explanation for the fever. He divided his cases into three groups in respect to fever type. Isolated rises in temperature lasting not more than 24 hours accounted for 66 per cent of his cases. Twenty-six per cent of the patients had a remittent type of fever lasting from two days to two weeks with normal periods in between. The least common type of fever was the persisting, septic type lasting for weeks. This represented 7.7 per cent of the patients. Singer and Steigmann[19] stated that fever in malignant neoplasia, especially in gastric cancer, is of two types: (1) irregular intermittent or remittent giving rise to a clinical picture of septicemia of unknown origin; and (2) more or less regularly intermittent fever associated with chills and sweats simulating malaria.

The relationship between metastases and fever has been mentioned. Some authors believe that fever is more frequent in metastatic cases with ulcerating lesions or liver involvement. Others have reported that no difference in fever is found between local disease and metastatic disease.

In regard to the etiology of fever in malignant neoplasms, most authors make no comment, or state that they don't know. Some interesting suggestions, however, should be mentioned. Bower[20] has made the observation that febrile patients with malignant neoplasia are suffering from one of two general conditions: (1) the presence of foreign substances in the blood stream, or (2) central disturbances of the thermoregulating centers in the thalamus. The regular

accompaniments of fever in cancer are elevation of the circulating white blood cells, anemia, muscles which are grossly dark in color, soft and flabby heart, and generalized loss of tissue turgor.

As early as 1878, physicians noticed that protein metabolism was increased in cancer and that the degree of temperature elevation frequently paralleled the increase in protein demand (Flüger).[21] This increase in protein requirement is stated to be independent of the normal "wear and tear" nitrogenous metabolism. Kocher[22] and Warburg[23] have repeatedly shown that tumor cells have a metabolism of their own which differs from that of normal cells. In their opinions this difference in the metabolism of normal and malignant neoplastic cells may cause the change in body economy that produces the variation in body temperature seen in cancer patients. They do not suggest any specific etiologic agent. Gordon[24] stated that the fever of malignant neoplasia is due to rapid growth and multiplication of carcinoma cells. He spoke of "growth fever" as a definite entity.

Fever as a rule is associated with some form of cell injury. Menkin[25,26] has shown that at the site of any cell injury, a proteolytic enzyme is present that converts damaged or "dead" proteins into an altered toxic protein, "pyrexin." His studies indicated "pyrexin" (a euglobulin bound or associated protein complex) to be present in all areas of cell destruction. "Pyrexin" is specifically active upon the thermoregulatory centers of the thalamus to produce elevation of body temperature roughly in ratio to the circulating "pyrexin" content. Smith and Smith[27] have found that circulating "pyrexin-like" agents bound to the euglobulin fraction are present in patients with cancer and fever as well as in normal menstruating women with fever. In his book, Voelcker[28] attributes fever in malignant neoplasia to the absorption into the general circulation of albumin bodies. These albumins were presumed to be end products of involuting cells resulting from rapid cell overgrowth with a relative lack of blood supply. In a similar vein, other workers[29] ascribe fever in cancer as an anaphylactoid response. They were not able, however, to show an immunologic pattern or specificity to support their hypothesis.

In a review of the literature on the subject of etiology of fever in 1895, Wassijeff[30] concluded that the evidence indicated that fever in carcinoma was due to toxic absorption from tumor cells, either from ischemic breakdown ("retrograde metamorphosis") or growth dissemination. Colman and Dubois[31] and Lusk[32,33] have made the observation that fever may be produced by severe toxic destructive end products of protein origin and points out that this situation

exists in tumors that grow more rapidly than their blood supply. Mandel[34,35] has presented evidence that degenerating carcinoma cells liberate purine bases that are capable of producing fever when introduced into normal animals.

Other workers believe that fever in patients with cancer has an infectious basis. Olmer[36] has made the statement that such fever is caused by an undiscovered septicemia, probably streptococcic. Several authors have pointed out that fever in malignant neoplasia might be due to septicemia made possible by a defect in the body lymphatics that have been compromised by metastatic disease. Fromme[37] postulated that this might be due to "mechanical damage of carcinoma." His thought was that large lymphatic routes are opened and numeorus bacteria are introduced into lymph glands, the barriers of which are overwhelmed by the combined tumor infiltration and bacterial localization. Eichenhorst[38] has pointed out that the common fever-producing tumors of the stomach, intestinal tract, and uterus are all situated where infection is invited and is frequent. He admits that he is "puzzled" by the fever seen in such "wholly aseptic" areas as in carcinomas of the adrenal, ovary, kidney and brain. Another group of workers have mentioned that "cellular septicemia" (circulating neoplastic cells) might be expected to produce fever much as circulating bacteria. Both circulating tumor cells and bacteria are foreign to the circulation and the body economy might be expected to destroy them with resulting fever.

Jackson[39] has thought the fever seen in malignant lymphomas was due to absorption of blood from capillary hemorrhages seen in this disease. Gemmill[40] comments that radiation attenuates malignant lymphomas without having any particular effect (clinically) on the fever of the disease but that remission of bleeding is regularly seen.

Percy[41,42] was interested in the relation of fever to cancer and published several articles. He states that 95 per cent of his carefully studied patients suffering from various forms of cancer did not have a fever characterized by a special degree of severity for the previous 25 years or more. He suggested that the most pronounced inhibiting influence in the development of cancer in human subjects seems to be connected in some way with a more or less severe pyrexia in the patient's earlier years. Vidal[43] has stated that of the methods of treating cancer with vaccines and toxins, all are attended by a reaction, the principal feature of which is fever, and when such a reaction is absent, no noxious action on the tumor occurs. Recently, several observations by persons interested in vital statistics have referred to the increased incidence of cancer and the

noteworthy present decrease of acute bacterial (fever-producing) disease in general. The infrequency of cancer in patients with tuberculosis is remarkable.

CASE. A 37 year old white female was admitted to the University of Kansas Medical Center on April 16, 1951, and dismissed on May 9. Her complaints were fever, cough, loss of weight and loss of appetite.

In November 1950, bilateral ovarian cysts and uterus were removed in this hospital. They were reported to be benign. She had been well until March 1951 when insidiously she began to have chronic fatigue, weight loss, and anorexia. For six weeks she had had a daily fever often as high as 101 to 103 F. A mass was discovered in her left lower abdomen by her family physician one week before admission. Since the onset of illness she has had a persistent cough with at times some mucopurulent sputum.

Examination: Pallor and weight loss were obvious. In the left lower quadrant, just above the pelvic brim, there was a firm smooth mass, non-tender, which was slightly movable, and measured 5 by 10 by 4 cm. There were a few pus cells in the urine. The hemoglobin was 8.6 Gm. and the leukocyte count was 15,000 per cu. mm. Serologic reactions were negative. Blood chemistries were within normal limits. Skin test was positive for histoplasmosis and negative for tuberculosis. Urine culture on two occasions revealed a moderate growth of Escherichia. Stool examination was negative on several occasions. Coombs test was negative. Agglutination studies for typhoid, paratyphoid, A and B, and Brucella were all negative. These were repeated and again were negative. Spinal fluid culture and examination were normal. Repeated blood cultures for aerobic and anaerobic organisms were

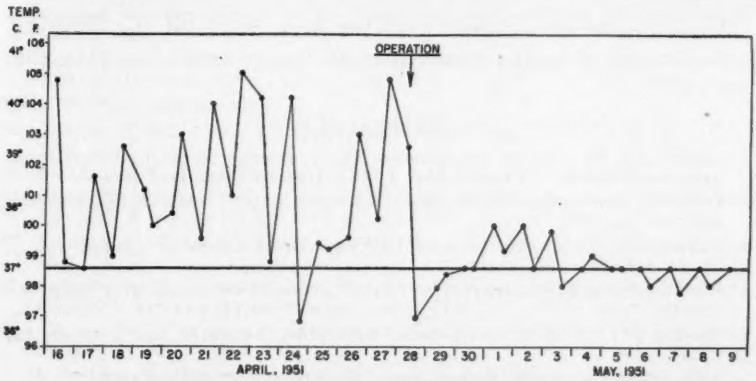

Chart 1. Showing minimum and maximum daily temperatures before and after removal of malignant abdominal tumor.

consistently negative. Daily sputum examinations and gastric washings were negative for tubercle bacilli. The consulting hematologist made a diagnosis of hypochromic anemia. Bone marrow studies were interpreted as myeloid hyperplasia of bone marrow. Roentgenogram studies of the chest and intravenous pyelograms were negative. A barium enema showed the sigmoid colon displaced to the right by a lower abdominal mass. No disease was found by

sigmoidoscopy. On April 28, 1951, a left lower abdominal retroperitoneal tumor was removed which measured 7 by 9 by 13 cm. It lay just outside of the true pelvis over the iliac vessels and was adherent to the mesosigmoid. There was no evidence of metastases. The pathological diagnosis was malignant tumor, type undetermined. There was necrosis and liquefaction of the central portion of the tumor. The postoperative course was quite uneventful. Her temperature which had gone as high as 105 F. daily preoperatively was within normal limits postoperatively except for a slight rise to the third day (chart 1).

Our roentgenologist advised roentgenologic therapy which was given after the patient left the hospital.

SUMMARY

The striking features of this case were the immediate drop in temperature to normal the day of operation and the prompt disappearance of the cough. The blood count rapidly returned to normal.

CONCLUSIONS

The literature of fever in malignant disease is reviewed and a striking case of fever associated with a rapidly growing abdominal tumor is reported.

The fever in the case recorded is attributed to necrosis of a rapidly growing tumor with absorption of degenerative products of protein.

No adequate explanation has ever been made of the chemical factors involved in the production of fever caused by malignant tumors.

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SERODIAGNOSTIC PROCEDURES FOR CANCER

Too frequently scientific articles claim to have found a new test for cancer of surprising accuracy, the newspapers extoll the discovery, handy diagnostic kits are advertised for sale to physicians and patients request the new miracle test. The medical practitioner must be prepared to answer his patients' questions and to differentiate the scientific observations from the unfortunate exaggerations.

The more effective control of cancer, a disease which claims over 200,000 lives each year in this country, awaits better methods of detection and early diagnosis and more effective therapy. The fact that over half of the cancer patients, exclusive of skin cancer, are not diagnosed before their lesions have progressed to the point where curative treatment is questionable or impossible attests to the need for developing improved methods for the diagnosis of cancer. While there is hope for improving this picture for the more superficial sites of cancer by educational means, this will not be true for cancer of less accessible sites until improved diagnostic procedures are available. With the exception of the tissue sites to which diagnostic cytology is applicable, there does not seem to be any

immediate prospect of substantial improvement in the demonstration of cancer lesions by present conventional technics. The visionary scientist and skeptic both agree that the discovery of an accurate serodiagnostic test for cancer, which would permit the recognition of early cancer or precancerous states, would be one of the most important advances in cancer control. Many scientists think the tremendous importance of the problem justifies continuing the research; the skeptics have already abandoned hope.

Cancer serodiagnostic procedures may have as their purpose either the detection of unsuspected malignant neoplasia in the general population or the aiding in the differential diagnosis in cases of suspected cancer. If a test with 100 per cent positive reactions in cases of early cancer and 10 per cent false positive tests in individuals without cancer were administered to the 40,000 persons over 35 years of age in a population of 100,000, who would be in the age group with the highest cancer incidence, one would find positive tests on approximately 250 people with early cancer and on 4,000 people without cancer. Thus it would be no small task for physicians to segregate the 250 cases of early cancer from the 4,000 people with false positive reactions for cancer. For consideration as a satisfactory detection test, it should have less than 5 per cent false positive and 10 per cent false negative results.

The requirements for a serodiagnostic differential aid for cancer are not necessarily as stringent as for detection of early unsuspected cancer. Although such a testing procedure might not help the masses of people, it could be most important to the sick patient suspected of having cancer.

Numerous attempts have been made to demonstrate the presence of a cancer by measuring some change in body fluids or excretions resulting from specific substances elaborated by the cancerous tissue, a specific immunologic or metabolic change produced in the host organism as a result of the presence of cancer, or some other manifestation of the interrelationship between the cancerous tissue and normal tissues of the host. Since there is no known chemical or physical property of cancer cells which is characteristic for them alone, one does not have as good a scientific basis as desirable for developing a suitable serodiagnostic procedure. Much of the past and present work has been done on an empirical basis. Such an empirical approach, which has yielded many important discoveries including the Wassermann serologic tests for syphilis, has merit when a better approach is not available.

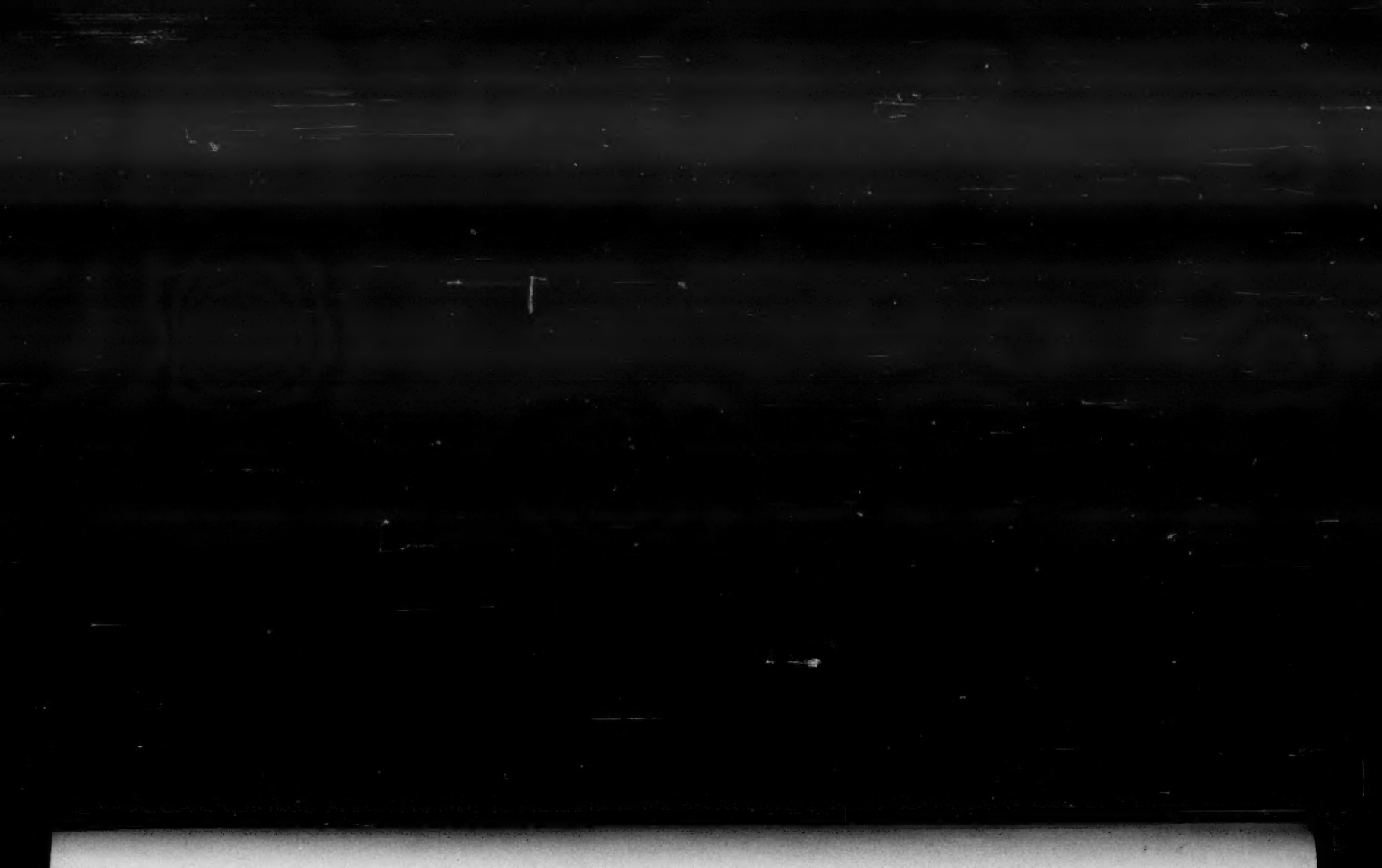
It seems more plausible that a diagnostic procedure may be developed for one type of cancer than for all malignant neoplasms.

All cancers may be no more a single disease than all infectious processes. Basal cell carcinoma of the nose and rhabdomyosarcoma of the thigh may have little more in common than do coryza and actinomycosis.

Of the many proposed tests, no serodiagnostic procedure for cancer has been consistently confirmed by the critical evaluation of other groups of investigators. In many instances the unsatisfactory results of these tests have not been reported in the literature. Only a few of these possible tests for cancer will be mentioned. For example Bolen has proposed a simple test for cancer based on alteration of the patterns of blood coagulation on a glass slide, but the results obtained in some other laboratories have been quite inaccurate. Tests for the degree of inhibition of serum protein heat coagulation by iodoacetic acid and modifications of such tests by Huggins and his associates have yielded more variable and unsatisfactory results in many laboratories. Black and collaborators have proposed that cancer can be diagnosed by tests of changes in reducing power of cancer sera for dyes such as methylene blue and by prolongation of time for heat coagulation of cancer plasma, but unsatisfactory results have been found by other workers. The serum flocculation test of Penn and associates has not been satisfactory in the experience of some workers from his own and other laboratories. The enthusiastic claims for the Roffo neutral red test and those for the Munro protective colloid test for cancer sera have not been confirmed. Most of these proposed tests are based upon physical and chemical differences in the proteins and other serum constituents which are not of specific significance with respect to malignant neoplastic disease. The results in carefully controlled experiments are often roughly comparable in accuracy to the blood sedimentation rate.

It is not easy to explain the differences obtained with such serodiagnostic procedures in various laboratories. Of major importance is the careful control of technics and the selection of suitable groups of (a) normal controls, (b) patients ill with non-neoplastic disease and (c) patients with cancer not complicated by other conditions. For several years the National Cancer Institute and other agencies have been supporting groups of investigators who have become experienced in the critical evaluation of such serodiagnostic tests and are maintaining facilities for such work. The conservation of funds and time of investigators and physicians would be substantial if future proposals of serodiagnostic tests could be promptly evaluated by several groups experienced in this type of research.

The physician's viewpoint on the possibility of developing serodiagnostic tests for cancer should remain conservative. The ulti-

mate goal of the prevention of cancer cannot be achieved until we have a better understanding of its etiologic factors. To date, no test has been confirmed as having sufficient sensitivity or specificity to be useful as a procedure for the diagnosis of cancer. However, many of these measurements seem to provide crude separations between some cancerous and noncancerous patients, and a well organized and continuing effort should be made until the possibilities for such diagnostic procedures as general tests for cancer or as tests for cancer of specific sites or type have been completely explored.

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